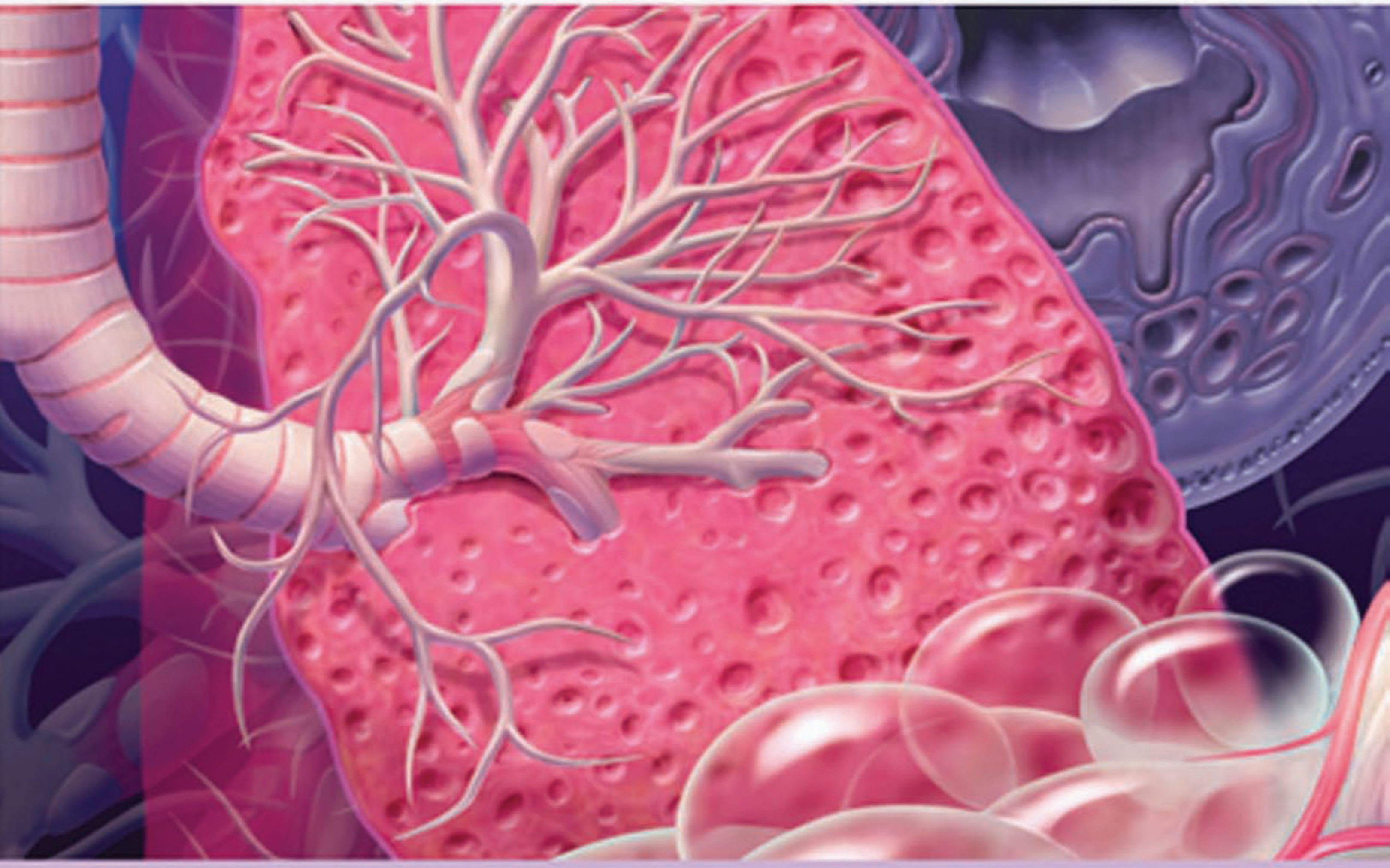
SEVENTH EDITION

PATHOLOGY ILLUSTRATED

ROBIN REID • FIONA ROBERTS • ELAINE MACDUFF



CHURCHILL LIVINGSTONE
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PATHOLOGY ILLUSTRATED

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PREFACE

'We believe that communication by verbal and written methods is the fundamental basis for study and learning. Nevertheless, in the modern setting where knowledge is increasing so rapidly and in a subject where morphological changes are a major component, we consider that the visual image has an important facilitating role'.

Since these comments were written in the preface to the first edition of 1981, undergraduate medical education has evolved greatly, notably in the widespread adoption of topic- or problem-based curricula and the generally diminished allocation of time, at least in a formal sense, to pathology.

We do not believe, however, that there has been any reduction in the importance of pathology as one of the foundations of clinical medicine.

In this seventh edition, the general layout and style of the book and its division into general and systemic chapters have been retained. The volume aims to be simple yet comprehensive and provide relevant information that can be assimilated in a reasonable time scale. We have concentrated on 'core' topics and on what we regard as clinically important pathology, not solely in 'Western' countries. Whilst including significant developments in each area we have tried to avoid 'information overload' not least in the vast field of molecular and cell biology. We recognize that our attempts at simplification do not tell the whole story.

We are indebted to our predecessors, Alasdair Govan, Peter Macfarlane, Robin Callander and Ian Ramsden, whose vision inspired the original concept of *Pathology Illustrated*. Much of their work from earlier editions remains with, we hope, appropriate modification. The credit for the book remains due to them; the shortcomings of this revision are our responsibility.

The most recent illustrations are the work of Graeme Chambers, to whom we are grateful. Many thanks are also owed to Carole McMurray, Development Editor at Elsevier for her considerable efforts in bringing this project to completion.

R. Reid
F. Roberts
E. MacDuff
Glasgow, December, 2010

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INTRODUCTION

Pathology is the study of disease. It describes the effects, progress and consequences of the disease and attempts to determine the cause (aetiology) and underlying mechanisms (pathogenesis). It forms a bridge between basic science and clinical practice and has traditionally had the same role in linking pre-clinical and clinical study for medical students.

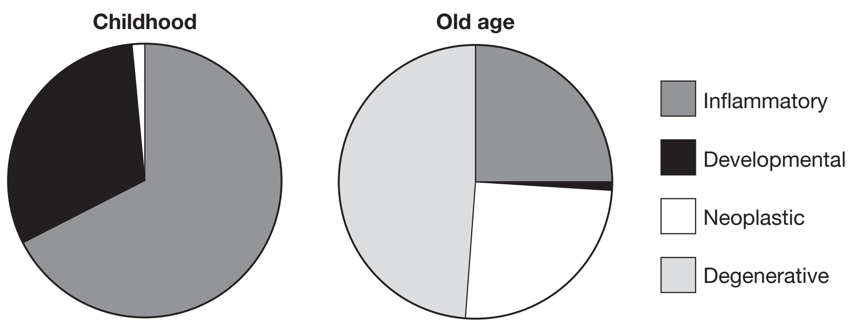
Disease occurs when there are variations of function or structure outside the normal range.

		Scientific study		Clinical Practice
DISEASE Variation outside normal range	→	PATHOLOGY (a) Causes (aetiology) including echanisms (b) Manifestations (c) Progress, sequelae	→	MEDICINE & SURGERY Diagnosis Prognosis Therapy and prophylaxis (including pharmacology)

The manifestations of the disease are the sum of the damage done by the precipitating cause and the body's response (which may be helpful or unhelpful or both). The variations in these components account for the great diversity of disease, which can then be classified into four main groups:

DEVELOPMENTAL   INFLAMMATORY   NEOPLASTIC   DEGENERATIVE

The relative importance of these groups varies with the age of the individual:



Different diseases affect different age groups. Developmental disorders and degenerative diseases affect the opposite extremes of life while tumours, in general, affect an ageing population.

Physiological ageing itself implies a gradual loss of cellular and body vitality usually associated with atrophy of tissues and organs. This process is aggravated and mimicked by the degenerative diseases of old age so that the physiological and pathological states tend to merge. Nonetheless, the student should attempt to identify the distinctions between ageing and disease. Additionally, in old age multiple diseases often coexist and interact with one another, and drug induced disorders are also common in this age group.

CAUSES OF DISEASE

The various factors involved are considered in two broad groups: 1) Environmental and 2) Genetic.

1. ENVIRONMENTAL FACTORS are numerous and can be classified under the following general headings:

Physical agents. Among these are trauma, radiation, both ionising and non-ionising, extremes of temperature, electrical power, i.e. the application to the body of excess (or insufficiency) of physical energy in any form.

Chemical poisons. Historically, these increased in importance with advances in industrial processing, but their effects have diminished by legislation to provoke safe working environments. Some, for example cyanide, are toxic to all tissues, while others target certain organs – paraquat affects the lungs and organic solvents damage especially the kidneys and liver. Others, for example strong acids and alkalis, act locally.

Iatrogenic diseases are an increasingly important subgroup as powerful drugs often have undesirable side effects, either predictably in a dose-dependent fashion or in an unpredictable idiosyncratic manner.

Nutritional deficiencies and excesses. These may arise from an inadequate supply, due to interference with absorption, inefficient transport within the body or defective utilisation. The effects may be general in distribution as in starvation or in severe hypoxia or they may damage specific tissues, e.g. vitamin deficiencies. Dietary excess plays an increasingly important role in Western countries, the rapidly increasing prevalence of diabetes mellitus being noteworthy.

Infections and infestations. Viruses, bacteria, fungi, protozoa and metazoa all cause disease. They may do so by destroying cells directly, for example in malaria. Infection with HIV destroys T cells resulting in severe immunodeficiency which renders the individual susceptible to many other infections, often due to organisms of low virulence (opportunistic infections). In other infections, the damage is done by toxins produced by the infecting agent such as tetanus, cholera and diphtheria; these may have a general or local effect.

Abnormal immune reactions. The normally protective immune system can in certain circumstances become deranged and damage the individual. Hypersensitivity to foreign substances can lead to anaphylactic shock or to more localised but nonetheless potentially lethal disorders such as asthma. If the process of 'tolerance' by which the immune system recognises the body's own tissues as self breaks down, then autoimmune diseases such as thyroiditis and pernicious anaemia result.

Psychological factors. These cause and influence disease processes in several ways. Psychological stress may lead to mental illness, and may alter the individual's symptoms

and response to somatic diseases. They are important components of diseases caused by addiction such as alcohol, tobacco and drugs. Finally, it is thought that psychological factors may be causally related to diseases such as hypertension, coronary thrombosis and, perhaps because of its effects on the immune system, to ulcerative colitis. It is worth noting, however, that the importance ascribed to stress in the pathogenesis of duodenal ulcers became much less when the pathogenic effects of *helicobacter pylori* were discovered in the 1980's.

2. GENETIC FACTORS are the results of actions of single genes or groups of genes.

Research, including the human genome product, has lead to a rapid expansion in our knowledge. Both variations in 'normal' genes and mutations which radically affect the function of 'abnormal genes' influence the development of disease.

Normal genes. There is considerable genetic variation among individuals, both within and between races and even within families. These genetic polymorphisms strongly influence SUSCEPTIBILTY and RESISTANCE to disease. For example:

a) The susceptibility of fair skin to damage by ultra-violet light and the development of skin cancer is well known and the mechanism – lack of the protective pigment melanin – is obvious and presumably determined on evolutionary grounds.

b) The human leucocyte antigen (HLA) system is a complex of genes on chromosome 6 in which there is great allelic variation. An individual's HLA type strongly influences the development of many disorders, especially autoimmune diseases, and of course determines whether a transplanted organ from a potential donor will be rejected or not.

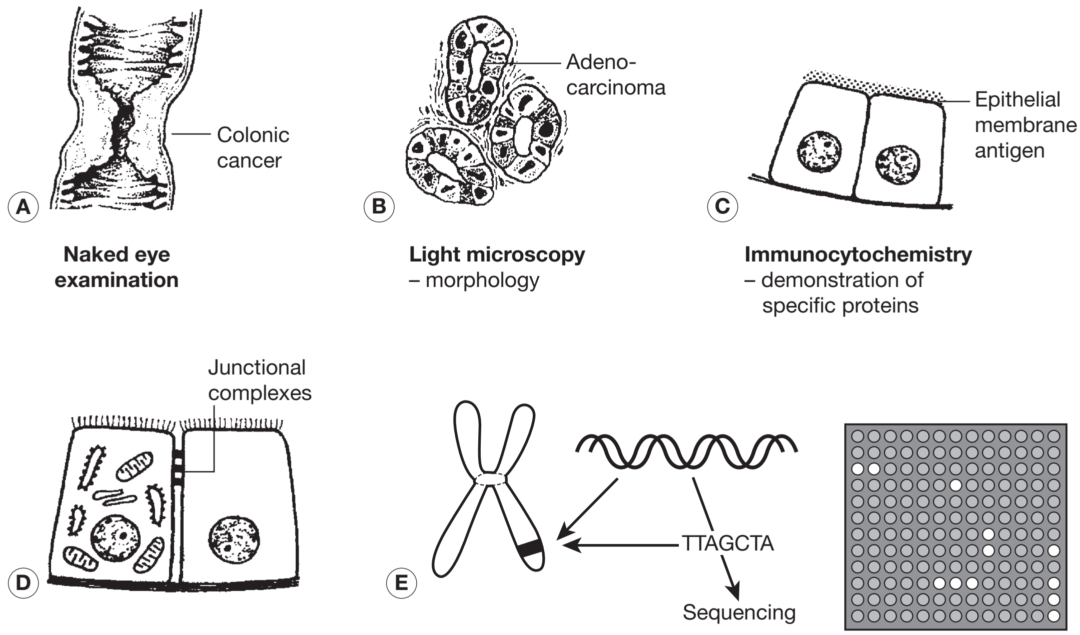
Abnormal genes. The mutations which give rise to disease vary from point mutations which affect a single base pair (e.g. sickle cell anaemia) through chromosomal translocations found in many tumour types such as Burkitt's lymphoma to the presence of an entire extra chromosome (e.g. trisomy 21 – Down's syndrome). Many mutations appear to arise spontaneously while others follow exposure to irradiation (in the survivors of Chernobyl and those who have received radiotherapy) or chemicals. Some mutations arise in the somatic tissues, whilst others are transmitted in the germline. These give rise to INHERITED diseases such as cystic fibrosis where the mutation directly determines the disease. In many other diseases, there is a genetic component, often contributed to by multiple genes, and an environmental contribution.

There is also variation in the rate at which mutations occur within individuals, often determined by variations in the genes responsible for DNA repair.

METHODS IN PATHOLOGY

The traditional methods of careful naked eye and light microscopic examination of organs at autopsy have been supplemented by the much wider use in clinical practice of biopsy and cytology where tissue or cells are removed during life for diagnosis.

Endoscopic and fine needle techniques allow biopsies to be obtained from most parts of the body. In addition, technological advances have allowed examination at more detailed levels:



Naked eye examination

Light microscopy – morphology

Immunocytochemistry – demonstration of specific proteins

Electron microscopy – organelles

Molecular biology – chromosomal analysis and chip technology

These increasingly sophisticated methods tend to influence the student to focus on detailed mechanisms at the molecular levels. It should not be forgotten that simple methods of gross examination and histological assessment are fundamental to the study of diseases. The following descriptions begin therefore with gross and microscopic pathology and proceed to the more detailed cellular changes when they are known. The student will find that such an approach is the basis of their learning in clinical practice.

CHAPTER 1

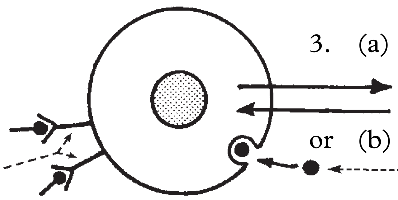
CELL AND TISSUE DAMAGE

CELLULAR PHYSIOLOGY AND PATHOLOGY

Understanding disease requires knowledge of cellular function and dysfunction.

Cellular physiology involves:
(a) Close relationships between cellular components and activities.
(b) Balancing control mechanisms to maintain constant conditions (homeostasis).
(c) Compensatory and repair mechanisms to minimise damage.

PLASMA MEMBRANES
Main functions.
1. Maintain integrity of cell.
2. Contact with extracellular environment, e.g. cell surface receptors.



3. (a) Passage of ions through permeable channels, e.g. Na^+, K^+
   or (b) Passage of complex molecules by pinocytosis or phagocytosis.

Membrane damage may lead to cellular dysfunction or death.

MITOCHONDRIA These are the main sites of ENERGY production.
Disorder of energy production affects all cellular functions.

Source	Production	Utilisation
	ADP → ATP	
O_2 + glucose →	(oxidative phosphorylation) → release of energy →	for all cellular activities

NUCLEUS
The nucleus controls all cellular activities through the action of at least 10 000 genes, each of which encodes a protein with structural, enzymatic or control functions.

Damage to DNA (e.g. by ionising radiation) is particularly likely in dividing cells. There are effective repair mechanisms but severe damage usually leads to cell death by apoptosis (see p.4).

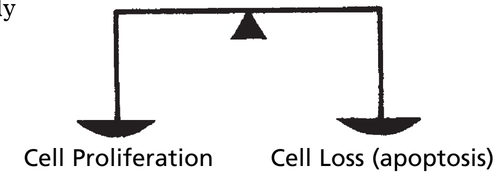
Germ cell DNA damage (i.e. to spermatogonia or oocytes)
1. Severe damage to chromosomal structure → Prevention of conception; Early abortion
2. Less severe damage to groups of genes or single genes → Developmental abnormalities; Hereditary disease; Susceptibility to diseases

Somatic cell DNA damage
This is acquired during life. Damage to stem cells is especially important.
The development of cancer (p.152) through activation of oncogenes or loss of tumour suppressor genes is the most important example.

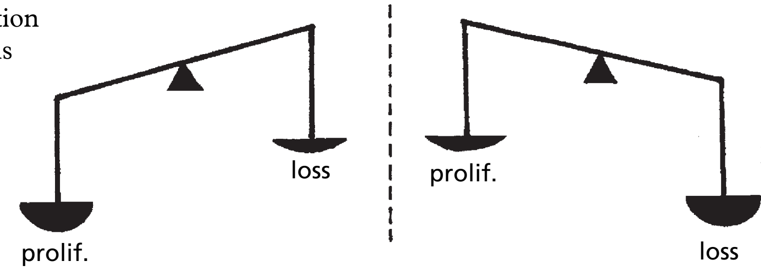
LYSOSOMES
These membrane bound organelles contain hydrolytic enzymes and are responsible for digestion and disposal of complex substances. → Disorder may lead to escape of enzymes or to accumulation of digestion products (e.g. storage disorders).

CONTROL OF CELL NUMBER

In adult life the CELL NUMBER is fairly constant. Complex control mechanisms evenly balance new cell production with cell loss.



During SOMATIC GROWTH cell proliferation outweighs cell loss.



In the ATROPHY of old age, cell loss outweighs cell proliferation.

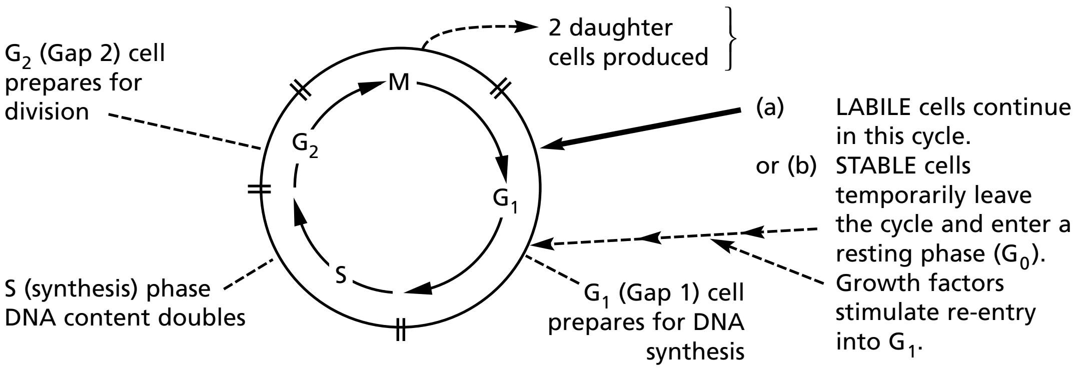
In many diseases the balance is lost.

Cell proliferation – the Cell Cycle

In adult life, cells can be classified into 3 groups according to their proliferation potential.

	Proliferation potential	Examples
1. LABILE CELLS	rapid proliferation and cell turnover	gut-lining epithelial cells
2. STABLE CELLS	slow proliferation and cell turnover	hepatocytes
3. PERMANENT CELLS	NOT able to proliferate	neurones

In preparation for division, a cell passes through 4 consecutive phases (G_1, S, G_2, M) ending in **Mitosis** (M).



A variety of growth promotors, inhibitors and drugs influence the cycle at various stages.

Knowledge of the cycle underlies the understanding of mechanisms involved in HEALING and REPAIR and in CARCINOGENESIS.

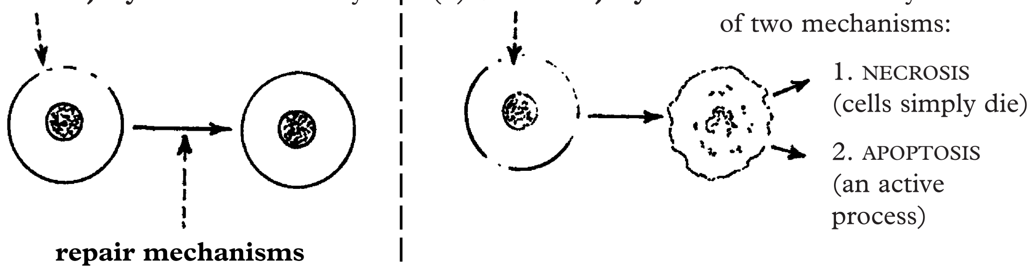
APOPTOSIS

A variety of noxious agents can damage cells. These include:

1. **Reduced oxygen supply** – respiratory disease, cardiovascular disease, anaemia
2. **Physical agents** – mechanical trauma, excessive heat or cold, radiation
3. **Chemical agents**
4. **Toxins** – bacteria, plants, animals (e.g. snakes)
5. **Viruses**
6. **Abnormal immunological reaction** – hypersensitivity states, glomerulonephritis
7. **Nutritional deficiencies** – vitamin deficiency and malabsorption syndromes
8. **Genetic abnormalities** – Down's syndrome.

The severity of the injury determines the outcome:

(a) **Mild injury** can be reversed by | (b) **Severe injury** results in cell death by one of two mechanisms:

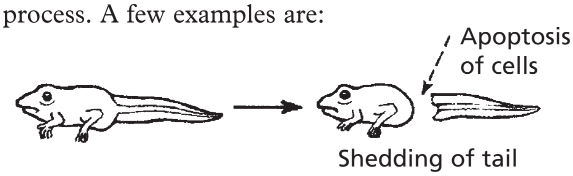


Apoptosis (programmed cell death) (Greek: apoptosis = falling off, like leaves from a tree) is an important process in health and disease by which, unlike necrosis (p. 5), abnormal or unwanted cells are eliminated. It involves activation of a programmed series of events co-ordinated by a dedicated set of gene products. It is an active process. A few examples are:

Apoptosis in health

In embryogenesis and development

(i) Metamorphosis of tadpole to frog.



(ii) Loss of autoreactive response of 'T' cells in the **thymus** preventing auto-immune attack.

(iii) In atrophy and involution, often on withdrawal of hormones, e.g. menstrual breakdown of endometrium.

Apoptosis in disease

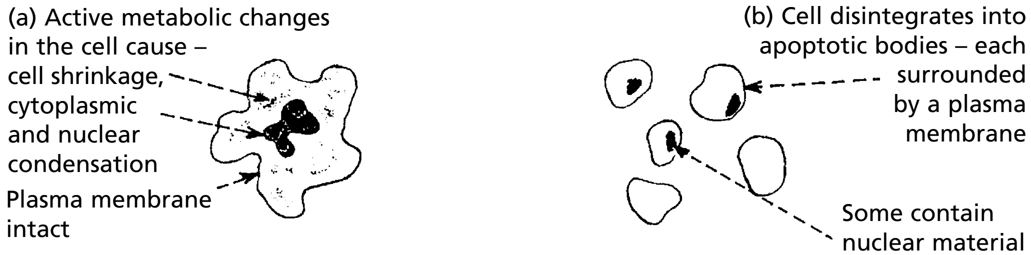
(i) Irradiation, (ii) Virus infection, (iii) Action of cytotoxic 'T' cells, e.g. in rejection of transplanted organs.

(iv) In tumours, apoptosis and proliferation rates together control the rate of tumour growth.

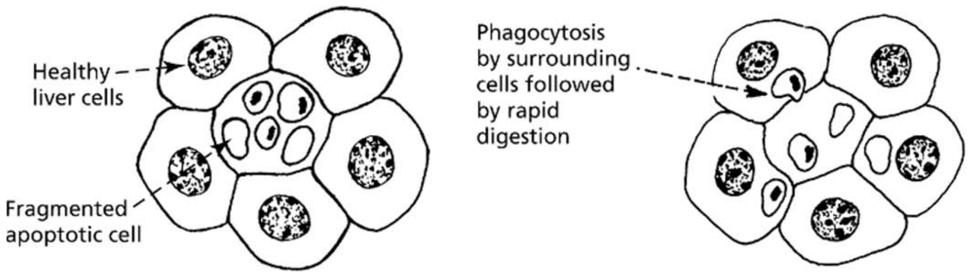
Apoptosis is a rapid process usually affecting SINGLE CELLS scattered in a population of healthy cells. It is considered in 2 stages:

CELL DAMAGE

Stage 1: **Cell death**



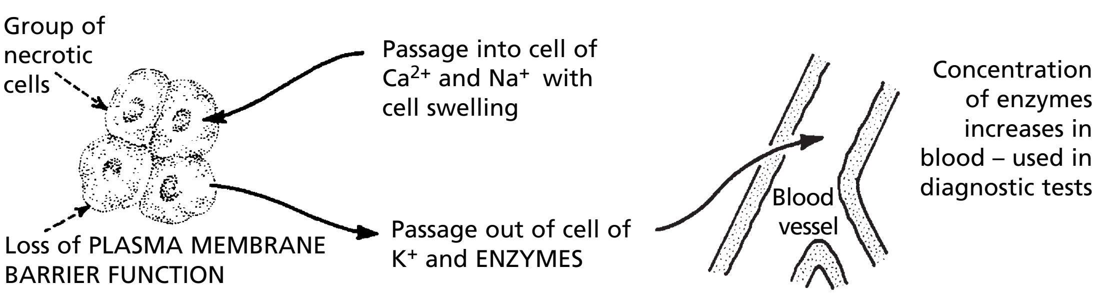
Stage 2: **Cell elimination**



1. The surrounding cells move together to fill the vacant space, leaving virtually no evidence of the process.
2. The plasma membranes around the apoptotic bodies remain intact.
3. There is no inflammation.
4. Apoptosis is tightly regulated by many genes including *ced* and *bcl-2.* These co-ordinate cell death through the control and integration stage and final execution phase.

NECROSIS

This term describes death of a cell or group of cells, typically following severe hypoxia, physical or chemical injury. Death of the cell is associated with rapid depletion of intracellular energy systems. Initially there are no morphological changes, but within a few hours the cell membrane and intracellular organelles are disrupted. Electron microscopy demonstrates these changes earlier than light microscopy.

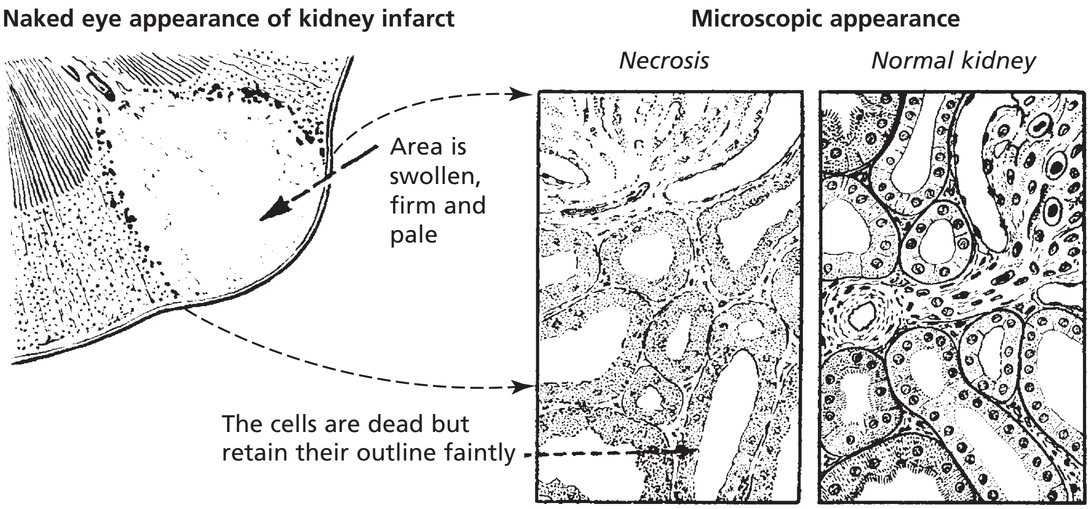


What we recognise as necrosis is due to denaturation and coagulation of protein and/or digestion of the cell by released enzymes. There are several naked eye appearances depending on which of these predominates.

NECROSIS

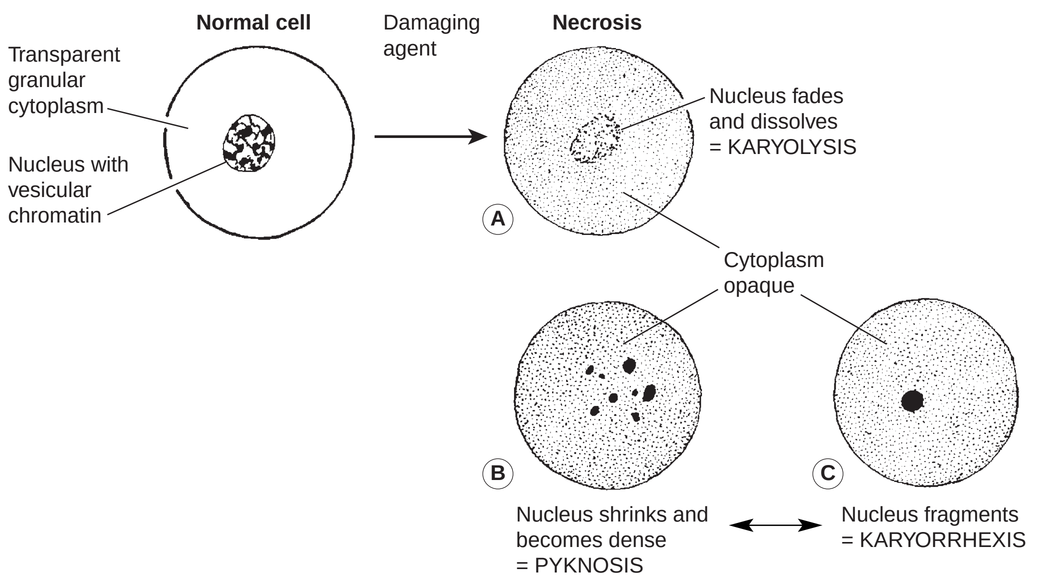
COAGULATIVE NECROSIS

This type of necrosis is frequently caused by lack of blood supply, e.g. infarcts of the heart, spleen and kidney.



The following changes are seen using the light microscope:

1. The nucleus shows one of three changes: (a) Karyolysis, (b) Karyorrhexis or (c) Pyknosis.
2. The cytoplasm becomes opaque and strongly eosinophilic (affinity for the red dye, eosin).



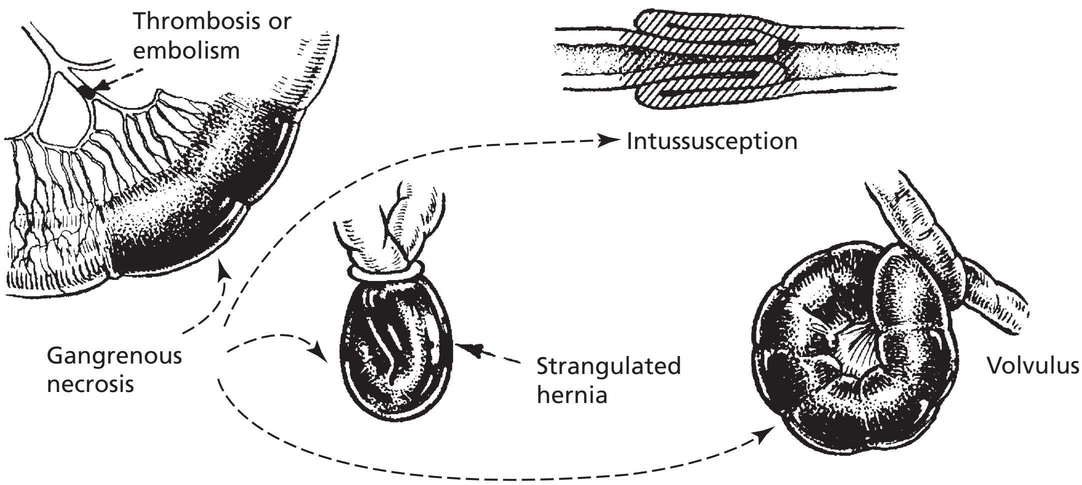
At *electron microscope (E.M.)* level, in addition to the above nuclear changes, disorganisation and disintegration of the cytoplasmic organelles and severe damage to the plasma membrane are seen with the formation of surface blebs.

NECROSIS

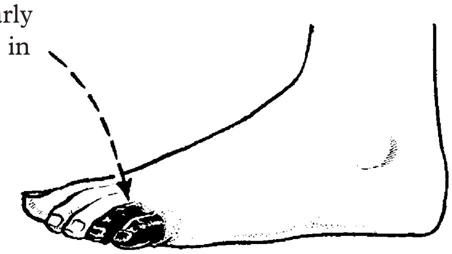
COLLIQUATIVE NECROSIS (LIQUEFACTIVE NECROSIS)
Death of cells in the brain result in liquefactive necrosis in which the dead cells are broken down to form a liquid mass. There is complete loss of structure (see p. 535).

An **abscess** (see p.39, 40) is another example of colliquative necrosis.

GANGRENE
This is a complication of necrosis, which occurs when tissues are invaded by bacteria which release proteolytic enzymes. These enzymes degrade the necrotic tissue releasing foul-smelling gases. The tissue becomes green or black due to breakdown of haemoglobin. Obstruction of the blood supply to the bowel, for example, is almost inevitably followed by gangrene:



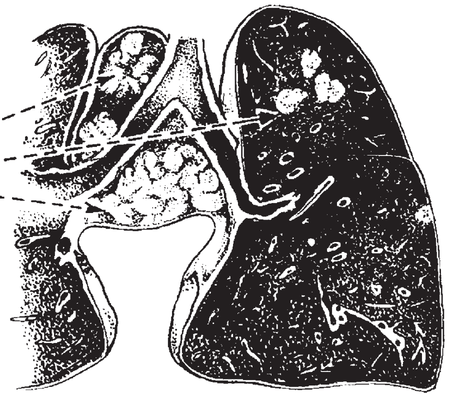
Gangrene also occurs on the skin surface following arterial obstruction. It is particularly liable to affect the limbs, especially the toes in diseases such as diabetes.



A special type of gangrene follows infection with clostridial organisms (gas gangrene; see p.70).

NECROSIS

CASEOUS NECROSIS
This is commonly seen in tuberculosis (p. 72). The necrotic tissue has a cream-cheesy appearance.



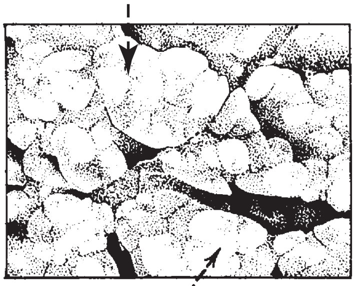
FAT NECROSIS
This is a descriptive term for a form of fat destruction seen, for example, in trauma and pancreatitis. The appearances are due to the action of lipases on triglycerides as follows:

TRIGLYCERIDES (released from necrotic fat) ⟶ FATTY ACIDS + Ca^{2+} ⟶ Insoluble SOAPS

↑ LIPASE usually pancreatic

Naked eye

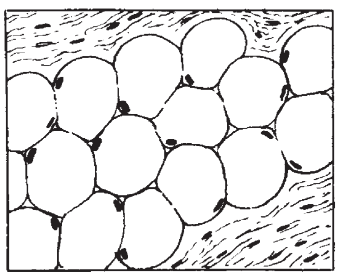
Fat



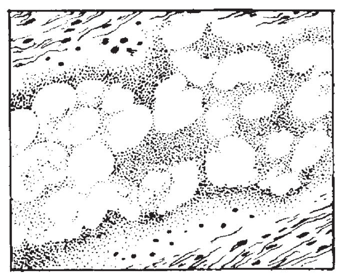
Opaque 'chalky' white patches

Microscopic

Normal fatty tissue



Necrotic



Loss of nuclei and cell structure

FIBRINOID NECROSIS
This is a descriptive term in which connective tissues and especially arterial walls are infiltrated by a strongly eosinophilic hyaline material which shows some of the characteristics of fibrin.

NECROSIS – AUTOLYSIS

SEQUELS OF NECROSIS

1. When small numbers of cells are involved, the cellular debris is removed by PHAGOCYTOSIS (see p.36).
2. With larger numbers of dead cells, there is an inflammatory response with organisation and fibrous repair (see p.40).
3. When the necrotic tissue cannot be completely removed or organised, deposition of calcium may be an additional feature, for example in TUBERCULOUS CASEOUS NECROSIS. This feature is important in radiological diagnosis. It is known as 'dystrophic calcification' (p.25).

AUTOLYSIS

The process of 'self-digestion' begins after the death of the cell (as described above) and proceeds at a rate dependent on the local enzyme content. The term is hence more commonly applied to the changes which take place in tissues removed from the body and in the whole body after death.

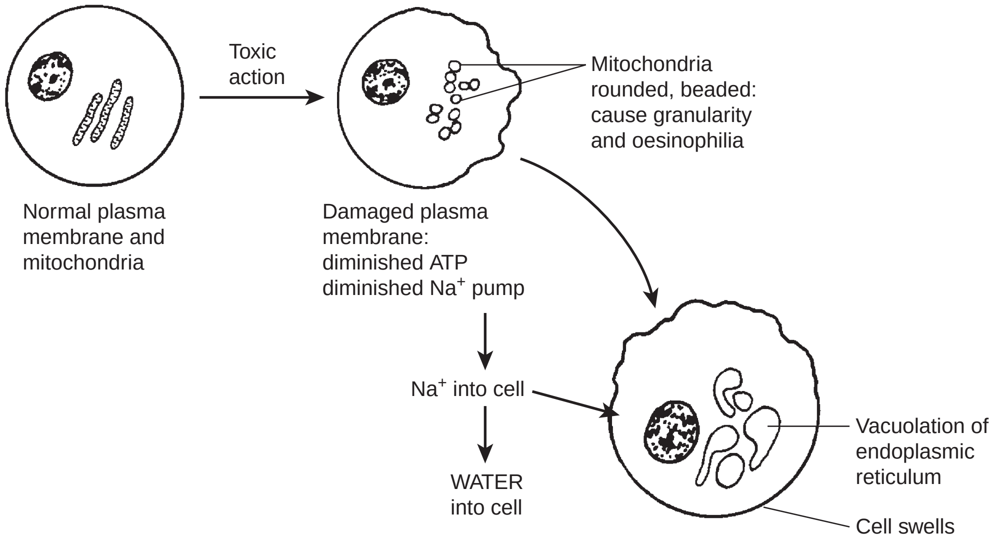
CELL DAMAGE – HYDROPIC SWELLING

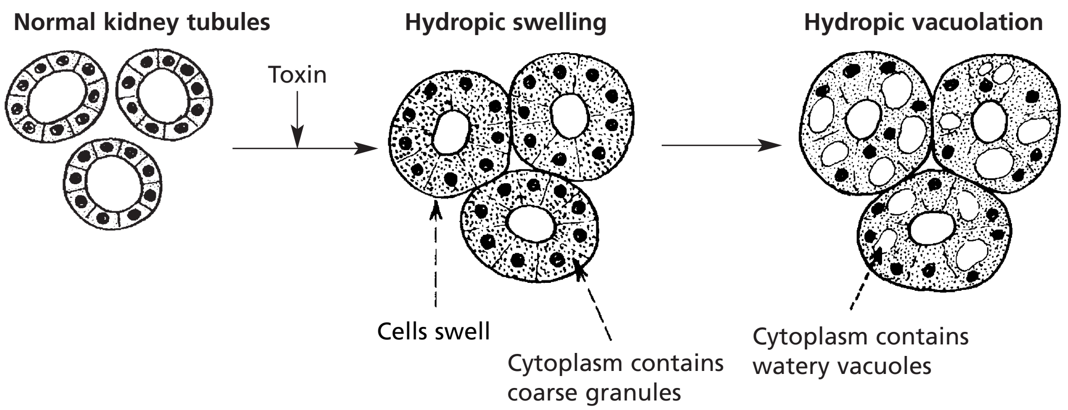
The various agents which can cause cell necrosis may also cause lesser cell damage which is reversible when the injurious agent is removed.

The appearances and effects are considered under these headings: 1. **hydropic swelling,** 2. **fatty change,** 3. **radiation** and 4. **atrophy**.

HYDROPIC SWELLING

Under the light microscope: Electron microscopic (EM) appearances indicate the mechanisms:





 Naked eye: The damaged organs become swollen and are pale.

CELL DAMAGE – FATTY CHANGE

FATTY CHANGE
This is accumulation of fat in non-fatty tissues, e.g. skeletal muscles and the heart.

These tissues cannot metabolise the amount of lipid presented to them, resulting in its accumulation within the cells. Examples include:

CELL POISONS
Bacterial,
Chemical, e.g. Chloroform, Alcohol.

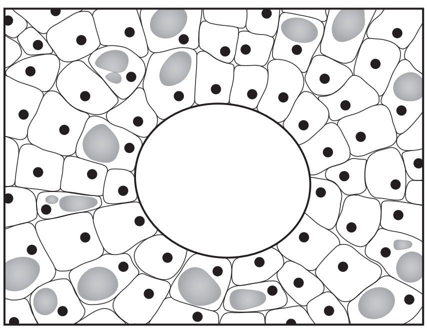
CLINICAL DISORDERS
Anoxia due to anaemia,
cardiac failure, respiratory disease.
Diabetes mellitus, Chronic malnutrition.

→ REDUCED cellular ENZYME activity → Inability to metabolise fat → Accumulation of fat in cells

In normal non-fatty tissues the intracellular fat is not visible by light microscopy using conventional fat stains.

In fatty change, the accumulated fat is visualised using frozen sections and fat-soluble dyes: e.g. Sudan, in routine paraffin sections the fat has been dissolved and is indicated by clear vacuoles.

For example, in the **LIVER**, the increase of deposited fat causes enlargement of the organ.



Macrovesicular steatosis

EFFECTS OF FATTY CHANGE
Impairment of cellular function is usually due to the pathological process causing the fatty change (e.g. anoxia in severe anaemia) and not to the physical presence of fat within the cell. In the liver, for example, very large accumulations of fat do not impair basic liver functions.

A possible exception is the myocardium in certain circumstances.

(a) **Rapid or large transfusion** → Increased ventricular pressure
+
Fatty myocardium → Weak muscle fibres
→ Dilatation of heart → Cardiac failure

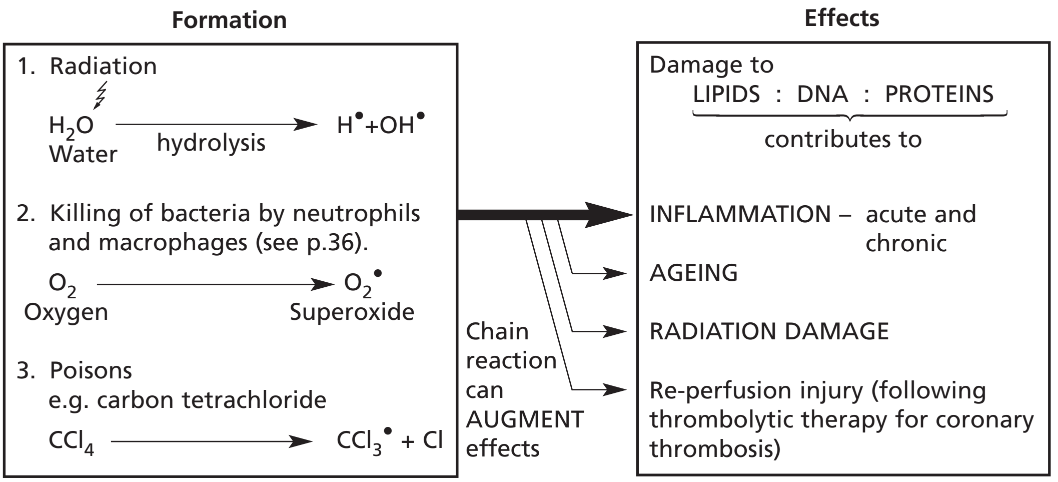
(b) **Sudden excessive exertion** → Rise in blood pressure
+
Fatty myocardium → Weak muscle fibres
→ Temporary left sided cardiac failure

CELL DAMAGE – FREE RADICALS

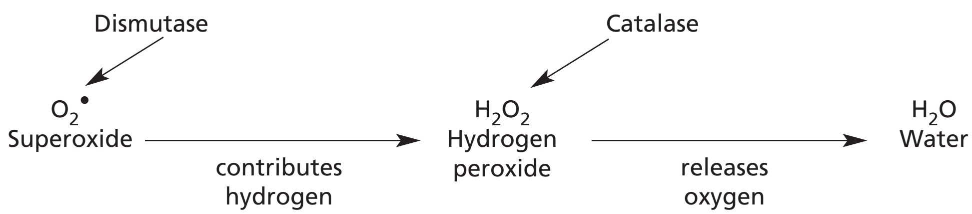
The formation of free radicals is an important contributory factor in many disease processes.

Free radicals are molecules with a single unpaired electron in an outer orbital position: they react with and modify a wide range of molecules, particularly lipids (of cell membranes), DNA and proteins.

A dot above the chemical symbol indicates the presence of a free radical:
e.g. $OH^{\bullet}$ = hydroxyl radical, $O_2^{\bullet}$ = superoxide radical.



Defence mechanisms to free radicals
Some free radicals decay spontaneously (e.g. $O_2^{\bullet}$) but they can also be removed by ANTIOXIDANTS (e.g. Vitamin E) and also by the action of enzymes such as superoxide dismutase and catalase.

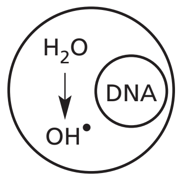


CELL DAMAGE – RADIATION

High energy (ionising) radiation, particularly in the form of gamma (γ) or X-rays can cause serious cellular and tissue damage. At cellular level there are 2 mechanisms involving:

1. The cell **CYTOPLASM**

   A large dose of radiation hydrolyses water producing damaging **free hydroxyl** radicals: acute cell death follows



2. The cell **NUCLEUS**

   Lower doses damage DNA with 2 results:
   (a) failure to replicate
   (b) mutation with genetic abnormalities

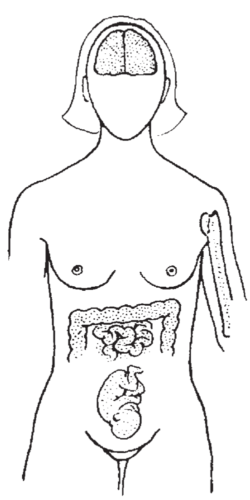
These effects will be considered under 3 headings:

1. The **localised effects** complicating radiotherapy in the tissues adjacent to the therapeutic field.
   There may be acute damage as well as later injury, following a latent period. This is caused by:
   (a) damage to blood vessels } leading to (a) *ischaemia*
   (b) damage to fibroblasts } leading to (b) *dense fibrosis*

   Injury to organs which are difficult to shield is seen, for example, in skin, eyes, alimentary tract, bladder, lungs, gonads and spinal cord.
   Wound healing is also seriously impaired.
2. Some of the mutations may lead to cancer, particularly leukaemias and lymphomas. (About 2% of all malignancies are associated with radiation.)
   The mechanisms are described on page 149.
3. **Whole body radiation** may result from nuclear explosion. The acute effects which are related to large doses are summarised below.

Note: Total body irradiation is used in treatment of some leukaemias.

Dose (Grays)	**Result**	**Mechanism**
above 50	Death in a few hours	All cells damaged but particularly **CNS:** CEREBRAL OEDEMA → COMA
5–10	Death 3–7 days	Mucous lining of **intestine** destroyed: DIARRHOEA: SEPTICAEMIC SHOCK
2–5	Death 2–3 weeks	**Bone marrow** destroyed: LEUCOPENIA THROMBOCYTOPENIA → INFECTION: HAEMORRHAGE
0.2–1	Damage to fetus in early pregnancy	Embryonal cell mutation

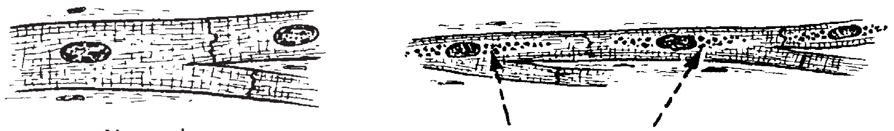


ATROPHY

This is a simple decrease in cell size or number, resulting in a shrinkage of affected tissues and organs. The most common example is atrophy of old age (see p.15).

Causes

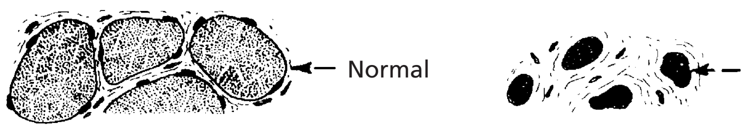
1. **Gradual diminution in blood supply** ⟶ Reduction in oxygen supply and nutrients ⟶ Fall in cell activity and shrinkage, e.g. narrowing of coronary arteries → myocardial atrophy



2. **Reduced functional activity** (disuse atrophy) ⟶ Diminished demand for nutrition ⟶ Atrophy of cells

   E.g. Lack of exercise ⟶ Atrophy of skeletal muscle
   E.g. Obstruction of gland duct ⟶ Atrophy of gland (Apoptosis is important here)

3. **Interrupted nerve supply** ⟶ Reduced reflex and metabolic activities, e.g. atrophy of skeletal muscles after destruction of motor nerves as in poliomyelitis.



4. **Endocrine deficiency** ⟶ Loss of trophic mechanism ⟶ Reduced metabolic activity in dependent tissues

   E.g. Pituitary deficiency ⟶ Atrophy of ⟶ Thyroid; ⟶ Adrenals; ⟶ Gonads and genital organs

5. **Pressure** ⟶ Interruption of blood supply and interference with function, e.g. neoplasm pressing on surrounding tissues.

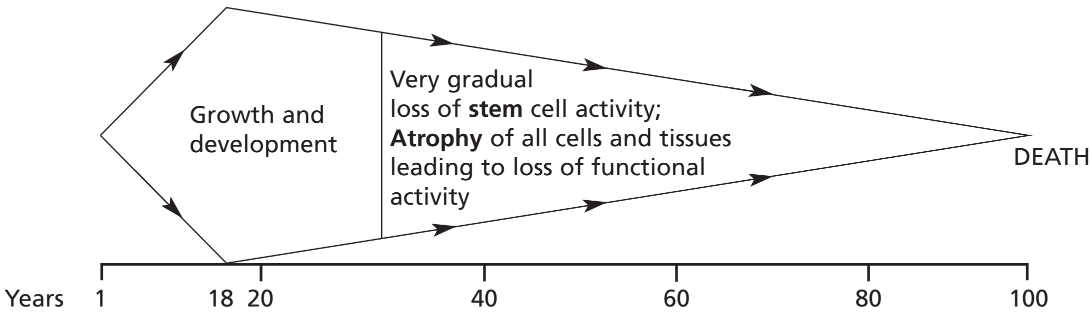
Atrophy is reversible provided the cause is eliminated or deficiencies restored.

AGEING

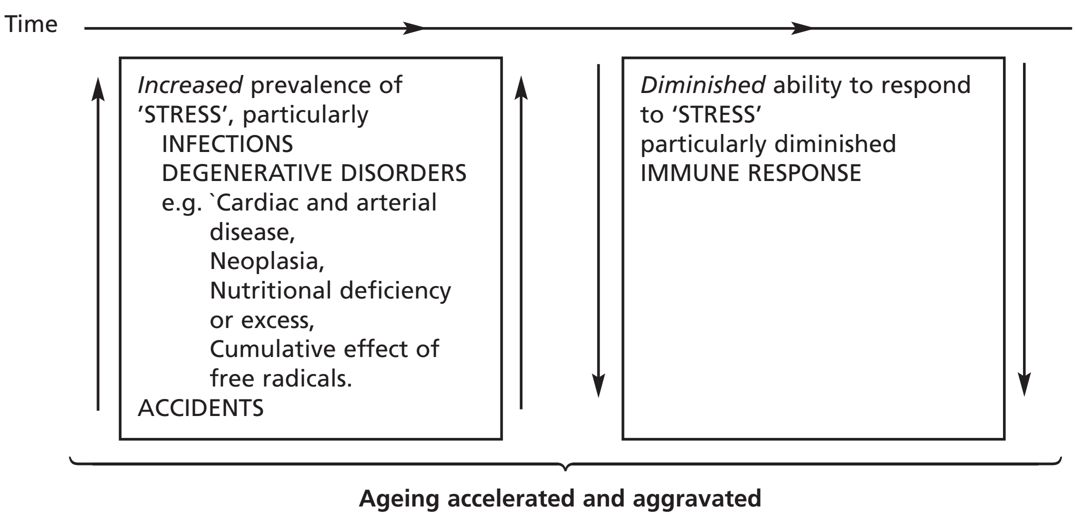
The distinction between 'true' ageing and ageing complicated by disease processes may be difficult; since therapy can be directed at the latter the distinction is important in clinical practice.

The changes associated with *true* ageing would be seen in a theoretical 'ideal' environment (minimal stress).

The following diagram is illustrative. The main controlling factors are *intrinsic*, i.e. genetic:
? associated with expression of ageing genes in mitochondria
? loss of cells' ability to divide due to telomeric shortening (ends of chromosomes).



In the real environment this theoretical concept of ageing is accelerated and aggravated by two groups of *extrinsic* factors:



Note: Death is only very rarely, if ever, due to 'pure' ageing. It is the result of disease – either a single process or, with increasing age, more often several causes.

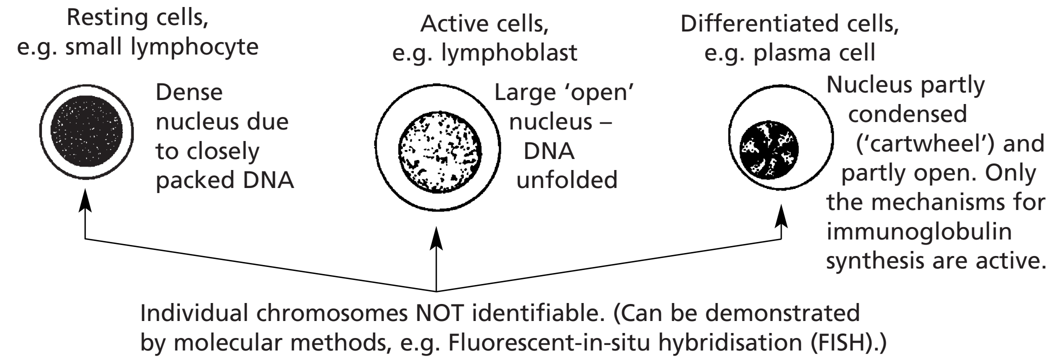
HEREDITY, GENES AND DISEASE

CELL NUCLEUS AND CHROMOSOMES

The cell **NUCLEUS** contains CHROMOSOMES, which transmit hereditary traits from one generation to the next and also control the synthesis of all the proteins in the body.

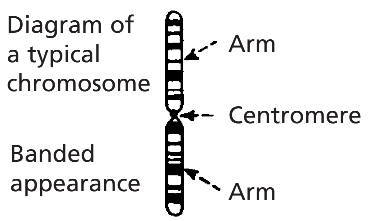
The 46 chromosomes which most human nuclei contain are not identifiable in differentiated cells or cells in the non-proliferating phase of the cell cycle (G_0).

The different morphological appearances of nuclei in histological sections indicate the amount of nuclear activity.



CHROMOSOMES

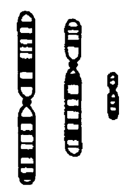
During MITOSIS the chromosomes condense into specific morphological forms which are identifiable by light microscopy: when colchicine is added to a cell culture, mitosis is arrested at the metaphase: chromosomes are then separable and can be studied.



Note: This appearance represents a very condensed and coiled molecular arrangement, i.e. inactive.

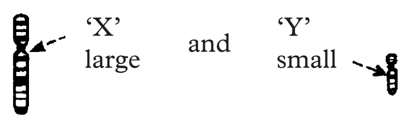
The following features are specific to each chromosome: 1. Overall length, 2. position of centromere (this dictates the length of each arm) and 3. the pattern of banding.

e.g.



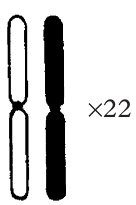
Using these morphological criteria each chromosome is identified and numbered 1 to 22.

The sex chromosomes are labelled

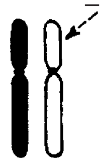


A typical normal chromosome map (karyotype) shows 22 pairs of different but identifiable chromosomes .... plus 2 sex chromosomes,

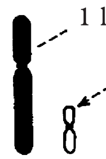
Each pair is called an AUTOSOME and consists of a PATERNAL and MATERNAL chromosome.



either 2 large X = FEMALE



or



HEREDITY, GENES AND DISEASE

DEOXYRIBONUCLEIC ACID (DNA)

Since Watson and Crick defined the molecular structure of DNA in 1953, there has been a great increase in knowledge of the 'genetic code'. Each chromosome is a very long single molecule of deoxyribonucleic acid (DNA), condensed during mitosis.

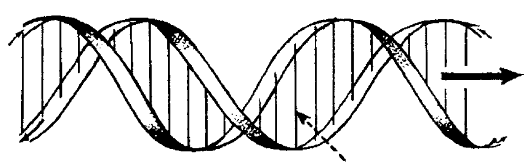


It is extended to its characteristic structure when active:

The **DOUBLE HELIX**

2 long spirals of nucleotides (consisting of a deoxyribose (sugar) + phosphate) around a central axis, complementary but running in opposite directions.

Diagram of a very small part of a very long molecule.



Joined by purine and pyrimidine base pairs

The function is to initiate and control the synthesis of proteins from amino-acids. All types of protein (structural proteins, hormones, receptors, intra-cellular messengers, etc.) are ENCODED along the molecule.

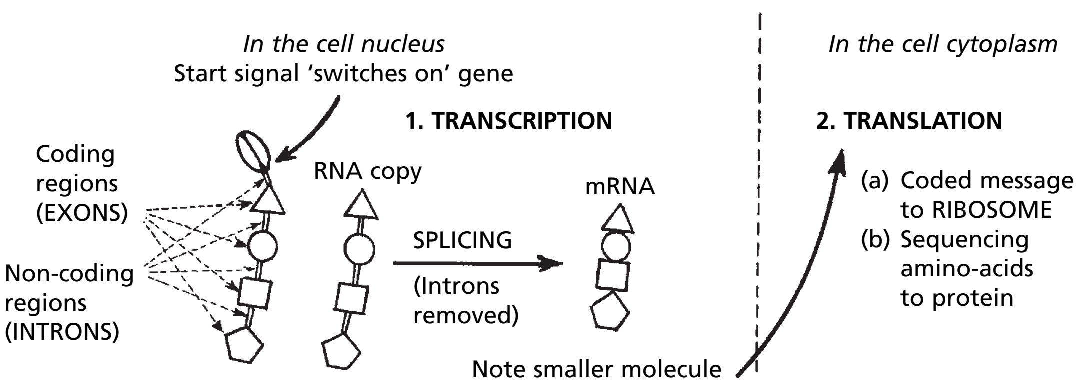
A **GENE** is the unit of the chromosome responsible for the synthesis of a single SPECIFIC PROTEIN. Genes vary in length but on average occupy about 20 000 base pairs of the molecule.

There are over 10 000 genes in all the human chromosomes, not all are active: some are repetitive: some form clusters subserving related activities (e.g. MHC (HLA) locus, see p.91).

There is a complex REGULATION of gene activity involving stop and start signals, promotor and enhancer functions all within the DNA structure. The entire human genome has now been sequenced.

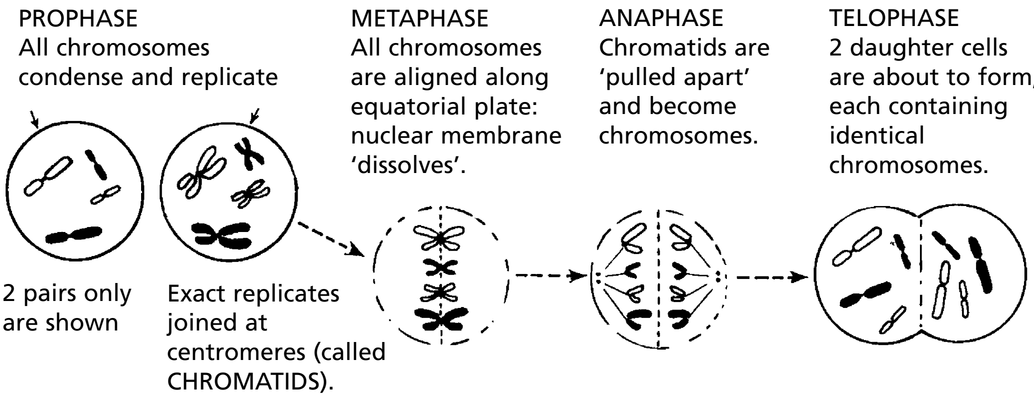
Gene expression and protein synthesis

A gene consists of coding regions (EXONS) interspersed with non-coding regions (INTRONS). In transcription the introns are eliminated and all the exons are transcribed to a ribonucleic acid form (mRNA) which is a copy of the DNA-code sequencing the amino-acids required for the production of a specific protein.



MITOSIS AND MEIOSIS

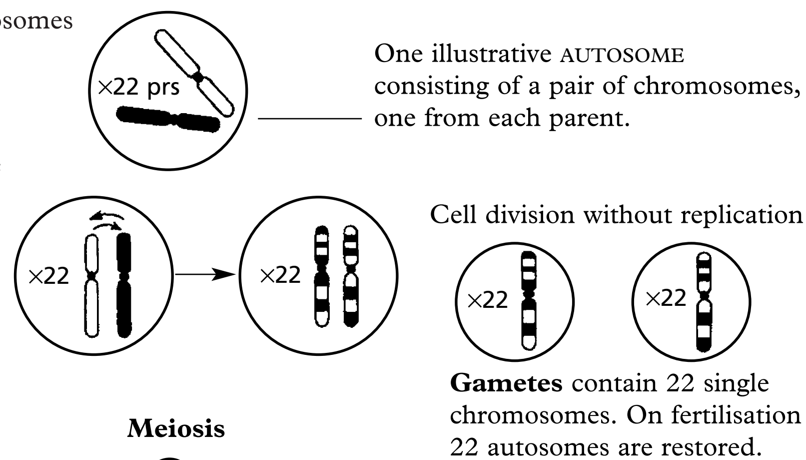
MITOSIS is the process by which SOMATIC cells proliferate ensuring *exact replication of the daughter cells*. Following the stimulus to proliferate, the chromosomes condense and replicate exactly.

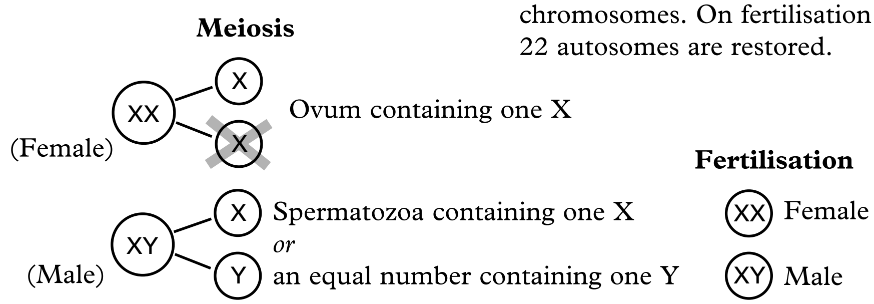


MEIOSIS is a complex process occurring during GAMETOGENESIS: it involves the reduction and division of chromosomes in such a way that: 1. a random mixture of both parental genes is present in the gamete and 2. the chances are equal for fertilisation to result in either sex. This simple diagram shows the important results of meiosis.

Primitive germ cell contains 46 chromosomes (i.e. 22 autosomes + XX or XY)

1. During MEOSIS the chromosomes come close together and random segments are exchanged
2. During MEOSIS the sex chromosomes are similarly distributed





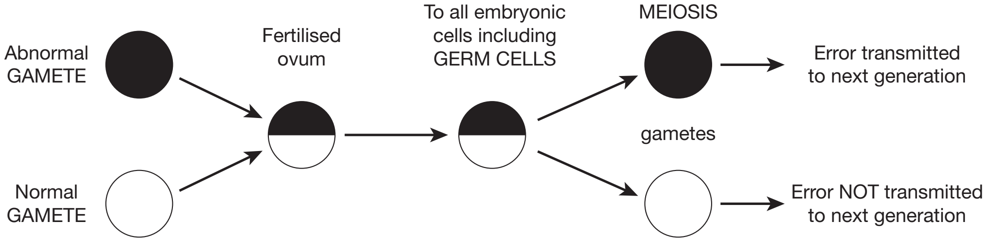
Note: In this simplified diagram a preliminary replication before meiosis and mitotic divisions after meiosis are omitted. The chances of error are greatly increased.

GENETIC ABNORMALITIES AND ASSOCIATED DISORDERS

It is not surprising that errors arise during these complex genetic activities. GERM CELLS and proliferating SOMATIC CELLS (including STEM CELLS) are susceptible to such errors.
They may occur spontaneously or be the result of external influences.
It is important to distinguish between germ cell and somatic cell abnormalities.

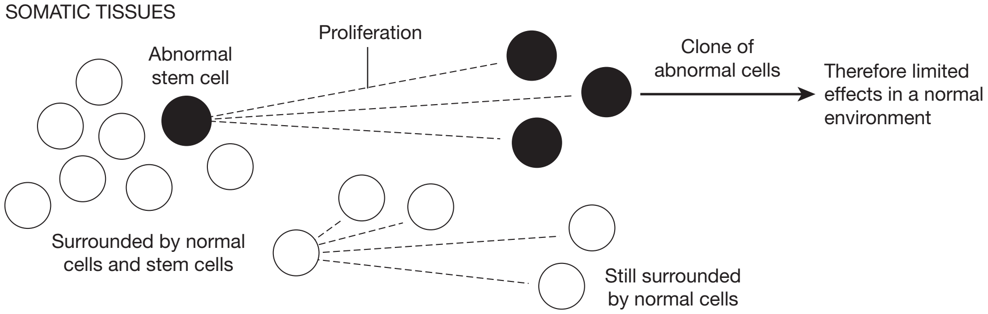
GERM CELL ABNORMALITIES

Errors which have arisen during germ cell development are transferred to the fertilised ovum and thence to all cells including the germ cells of the new individual.



ABNORMALITIES arising in SOMATIC CELLS

These tend to cause restricted effects: they are not transmitted to the next generation.



TYPES OF GENETIC ABNORMALITIES

They range from large, involving whole chromosomes, through parts of chromosomes, to gene clusters and single genes.

CHROMOSOMAL ABNORMALITIES

1. ***Polyploidy*** – when the chromosomal numbers are increased by an exact multiple of the normal (23) e.g. $23 \times 3 = 69$ chromosomes. Such nuclei are seen in hypertrophied muscle cells and ageing liver cells (i.e. somatic cell polyploidy).
   Such gross chromosomal abnormalities occurring during gametogenesis or at fertilisation are usually incompatible with life and are a common cause of spontaneous abortion.
2. ***Aneuploidy*** – where the number of chromosomes is increased usually by one (TRISOMY) or decreased by one (MONOSOMY). Early spontaneous abortion is again common: survivors show mental retardation and varied physical abnormalities.
   Down's syndrome is a good example of AUTOSOMAL TRISOMY and is due to an extra chromosome (i.e. Trisomy 21 – karyotype 47XX + 21 or 47XY + 21).
   The abnormality occurs in utero after fertilisation of the ovum and is therefore autosomal. Increasing maternal age is a potentiating factor in Down's syndrome and many other genetic defects.

GENETIC ABNORMALITIES AND ASSOCIATED DISORDERS

CHROMOSOMAL ABNORMALITIES *(continued)*

3. ***Structural abnormalities***
   Despite the existence of efficient repair mechanisms structural errors do arise when the long DNA molecules are accidentally broken during the physical changes occurring at replication. They include, for example, duplication and deletion of gene clusters and single genes: and translocation of fragments of DNA between chromosomes.

SINGLE GENE DISORDERS

Factors regulating the production of the final specific protein are extremely complex.

1. *In the nucleus* — *In the cytoplasm*

Activity of other genes ↓ promotion, enhancement, start/stop signals → single gene activity (including RNA transcription and movement) → ↑ *or* ↓ ← detailed control of each step in protein synthesis

↓ Therefore GENETIC EXPRESSION very VARIABLE

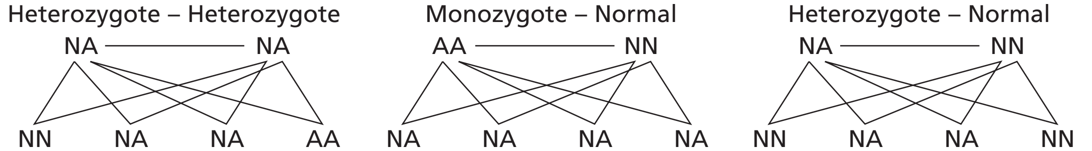
2. The corresponding genes on each parental chromosome exert important influences on each other. The inheritance of the Rhesus blood group D is a good example: there are two possibilities at the D locus on the chromosome – 'D' or 'd'. The 3 possible combinations give rise to the actual blood group (phenotype) as follows:

	Homozygous		Heterozygous	
Genotype	DD	dd	Dd	→ The presence of one D confers the
Blood group (phenotype)	D	d	D	blood group D i.e. D is DOMINANT.

d → The presence of two d's is required to confer the blood group d, i.e. d is RECESSIVE.

This concept is important in *inherited single gene disorders.*

1. In DOMINANT inheritance any HETEROZYGOUS offspring bearing the abnormal trait will be affected: mating with a normal partner statistically produces 50% of normal offspring and 50% affected.
2. In RECESSIVE inheritance only HOMOZYGOTES for the trait are affected. Such cases usually arise from the mating of 2 heterozygous CARRIERS who, by definition, are themselves unaffected.
   The results of mating are as follows: (A = affected gene, N = normal gene)
   NN = normal individual; NA = carrier; AA = affected individual.



Statistically 1 normal, 2 carriers, 1 affected

All offspring are carriers.

2 are normal, 2 are carriers.

GENETIC ABNORMALITIES AND ASSOCIATED DISORDERS

The concept of dominant and recessive traits is useful in genetic counselling. Long lists of dominant and recessive disorders are available: only a few important examples are given.

Autosomal dominant – neurofibromatosis, Huntington's disease: polyposis coli: congenital spherocytosis.

Autosomal recessive – cystic fibrosis, congenital deafness, mucopolysaccharidoses.

Sex-linked disorders are usually recessive and are carried on the X-chromosome: males are affected and females are carriers. Important disorders are haemophilia and muscular dystrophy.

METABOLIC DISORDERS (inborn errors of metabolism)

These are inherited disorders of single genes which code for the enzymes concerned in many metabolic pathways. The clinical effects show considerable variation in severity.

Examples are: disorders of carbohydrate (including glycogen storage), lipid and amino-acid metabolism: lysosomal storage: and membrane transport (including cystic fibrosis).

Note: Not all single gene abnormalities cause, by themselves, significant pathological effects. As indicated above, the controlling factors are complex and include the important effects of 'modifying genes'. It seems likely that abnormal recessive genes exist in the normal population but only present as clinical disorders in rare circumstances.

MULTIFACTORIAL DISORDERS
Most human diseases have a genetic component but environmental factors usually play a very important part in the pathogenesis.

COMBINED ACTIVITY of SEVERAL GENES (both normal and abnormal) + ENVIRONMENTAL FACTORS ⟶ DISEASE

Examples are: atopic (allergic) disorders: diabetes mellitus, hypertension, rheumatoid arthritis and various infections.

SOMATIC CELL GENETIC DISORDERS
When mutation occurs after fertilisation of the ovum and at any stage throughout life the effects are limited to the disordered cell(s) and progeny. The clinical effects tend to be localised.

NEOPLASMS and hamartomas are examples of somatic cell genetic disorders (see Carcinogenesis).

Note: In the systematic section of this book significant genetic contribution to the pathogenesis of diseases will be recorded.

AMYLOID DEPOSITION

Amyloid is a waxy substance deposited in the extracellular tissues, particularly around blood vessels and in basement membranes. Various forms of amyloid are seen and they have varying effects. Amyloid is resistant to degradation and its deposition tends to progress relentlessly.

Nature of Amyloid

Chemical: amyloid fibrils are made up of:

(i) A major variable component >90%.

(ii) A minor constant component, AMYLOID P PROTEIN – a glycoprotein normally found in serum.

Whatever its composition, amyloid fibrils are arranged in a β-pleated configuration: this accounts for its resistance to degradation and its staining properties.

Detection

To the naked eye, the affected organs are pale, enlarged and have a firm, waxy texture.

STAINING with LUGOL's IODINE
- AMYLOID – DEEP BROWN
- NORMAL – YELLOW

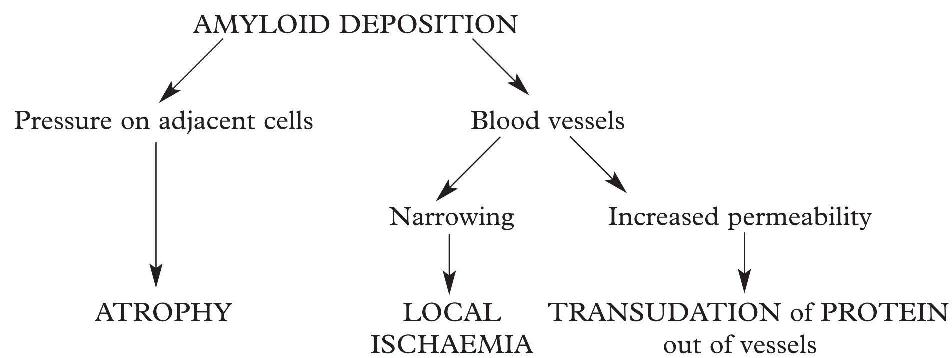
On light microscopy

(a) CONGO RED STAIN
- AMYLOID – RED STAINING: APPLE GREEN BIREFRINGENCE in POLARISED LIGHT.
- NORMAL – PALE PINK: NO BIREFRINGENCE.

(b) IMMUNOSTAINING – for specific constituents (e.g. P protein).

On electronmicroscopy – closely packed interlacing fibrils 70–100 nm in diameter.

Pathological effects



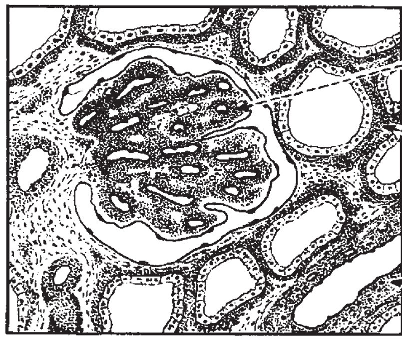
AMYLOID DEPOSITION

Almost any tissue in the body may be affected by amyloid deposition, but the most important changes occur in the kidney, gastrointestinal tract and the heart. Other organs, such as the liver and spleen, may also be grossly affected without serious functional impairment.

KIDNEY

In severe cases the kidneys are pale, firm and waxy, and with the iodine test the glomeruli stand out as brown dots to the naked eye.

Renal biopsy is useful in the diagnosis of amyloidosis.



Effects: Glomerular capillary permeability altered

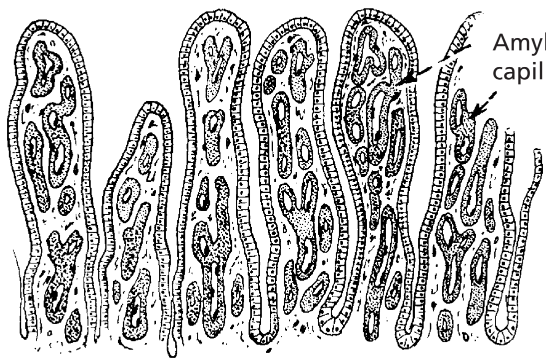
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GROSS PROTEINURIA ⟶ NEPHROTIC SYNDROME ⟶ late renal failure

GASTROINTESTINAL TRACT

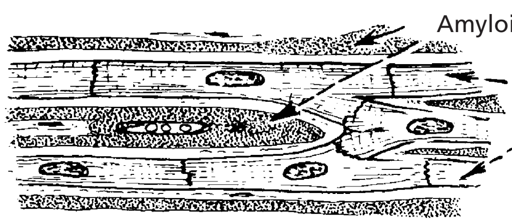
Due to altered permeability of the capillaries, the patient suffers from diarrhoea and protein loss. There may also be malabsorption, nutritional deficiencies and electrolyte imbalance.

Rectal biopsy is useful in the diagnosis of amyloidosis.



HEART

Amyloid deposition occurs around the cardiac muscle fibres and the capillary basement membranes. The heart is enlarged with thick walls. Much of the thickness is due to amyloid deposition.



Effects: Cardiac failure develops mainly due to the mechanical effect of amyloid, making the heart muscle stiff and preventing cardiac filling (restrictive cardiomyopathy). The blood supply to the muscle fibres is also impaired.

AMYLOID CLASSIFICATION

1. **SYSTEMIC AMYLOIDOSIS**

(a) *Associated with monoclonal plasma cell proliferation*
(e.g. myeloma, monoclonal gammopathy, Waldenstrom's macroglobulinaemia).

Increased production of:
Variable protein – AL (Amyloid Light chain derived) – from fragments of immunoglobulin, especially lambda light chains.

(b) *Associated with chronic inflammation*
(e.g. tuberculosis, osteomyelitis, rheumatoid arthritis, bronchiectasis and the genetically inherited familial Mediterranean fever.).

Increased production of:
Variable protein – AA (Amyloid A protein) – derived from serum AA protein, an acute phase reactant in many inflammatory conditions.

Summary of formation of amyloid

Abnormal (monoclonal) proliferation of plasma cells
↓
Abnormal immunoglobulins esp. lambda light chains
↓ ← Proteolysis
'Major variable component'
AMYLOIDOGENIC PROTEIN > 90%
(AL)
+ Amyloid P glycoprotein < 10%
↓
SYSTEMIC AMYLOID (AL)

Long continued active inflammation
↓
Acute phase reactant protein
↓ ← Proteolysis
'Major variable component'
AMYLOIDOGENIC PROTEIN > 90%
(AA)
+ Amyloid P glycoprotein <10%
↓
SYSTEMIC AMYLOID (AA)

2. **LOCALISED AMYLOIDOSIS**

In ENDOCRINE TUMOURS – amyloid derived from polypeptide hormones, e.g. medullary carcinoma of thyroid – calcitonin derived amyloid.

In OLD AGE – the amyloidogenic protein is related to pre-albumin. Deposits of amyloid occur in the heart, brain and joints. In Alzheimer's disease (p.544) local amyloid deposition in the brain is important.

CALCIFICATION

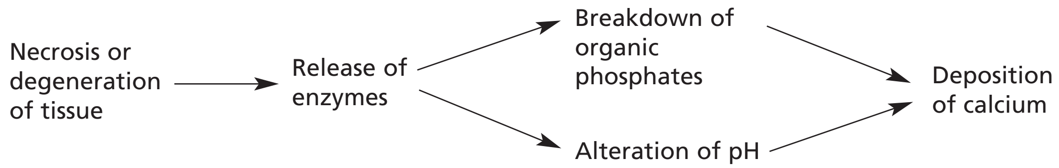
Abnormal deposits of calcium occur in 2 circumstances: dystrophic calcification and metastatic calcification.

1. DYSTROPHIC CALCIFICATION

Local deposits of calcium may occur in:

(a) **Necrotic tissue -** old caseous lesions of tuberculosis; old infarcts; collections of pus; in fat necrosis associated with pancreatitis.
(b) **Tissues undergoing slow degeneration -** hyaline areas in benign tumours (e.g. fibroids (p.501)); in arteries due to atheromatous degeneration or in old age; in old thrombi; diseased or abnormal heart valves.

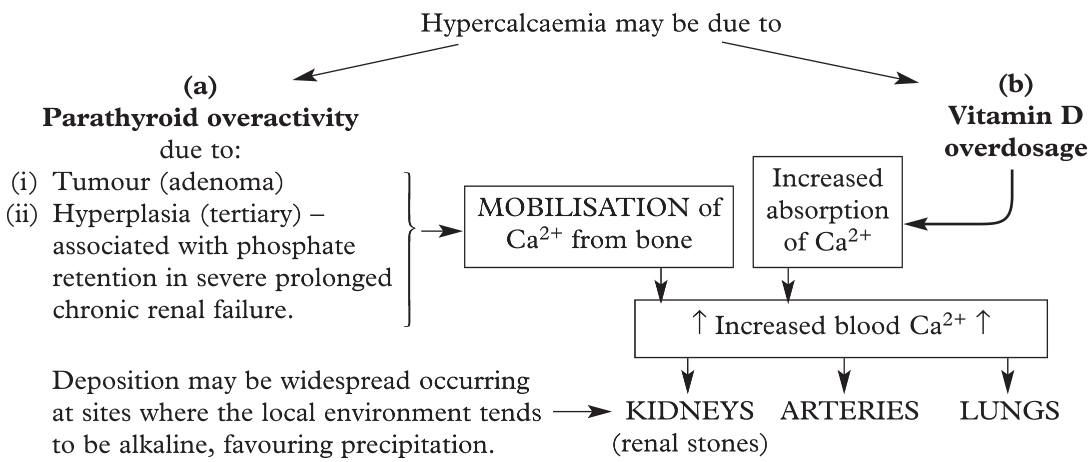
The mechanism may be as follows:



Note: Ca^{2+} is radio-opaque and therefore can be seen on X-rays where it is of diagnostic use, e.g. in old healed disease (e.g. tuberculosis) and also in some tumours, e.g. breast cancer where very small deposits of calcium may be present.

2. METASTATIC CALCIFICATION

In this case there is an increase in the calcium phosphate product in the blood (usually hypercalcaemia).



Some malignant tumours, e.g. breast and lung, are associated with hypercalcaemia and metastatic calcification.

The mechanisms are: 1. secretion by the tumour of a protein (parathyroid hormone related peptide (PTHrP)) which mimics the action of parathormone and 2. the local release of bone resorbing cytokines by tumour metastases in bones.

ENDOGENOUS PIGMENTATION

IRON-CONTAINING PIGMENT

Two main pigments are derived from the breakdown of red blood cells:
1. HAEMOSIDERIN and 2. BILIRUBIN.

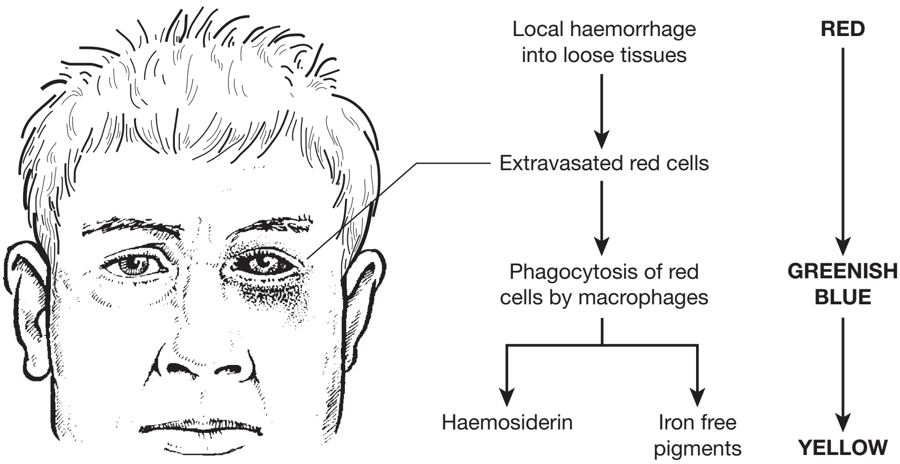
The detailed mechanism is described on page 340 in relation to JAUNDICE.

HAEMOSIDERIN

The iron derived from red cell breakdown is held in the spleen, liver and bone marrow, combined with apoferritin. In the plasma it is transported by transferrin. The two mechanisms maintain an equilibrium between the iron contents in these three sites. When the amount of iron within the cells becomes excessive and overloads the ferritin system, it is deposited in a brown granular form – haemosiderin. This occurs in 2 situations:

1. **Local breakdown of red cells in tissues, e.g. in a bruise**

The colour changes in a 'black' eye exemplify this mechanism



2. **Iron overload in tissues**

(a) *Haemosiderosis*

This is seen in the liver, spleen and sometimes the kidneys in cases of haemolytic anaemia, and in patients requiring repeated blood transfusion. The change is most dramatic in the liver, which becomes deep brown. Iron is found in the Kupffer cells first and, later, in liver cells. A Perl's stain highlights the iron deposits, which are stained blue. Iron deposits *per se* very rarely cause organ damage.

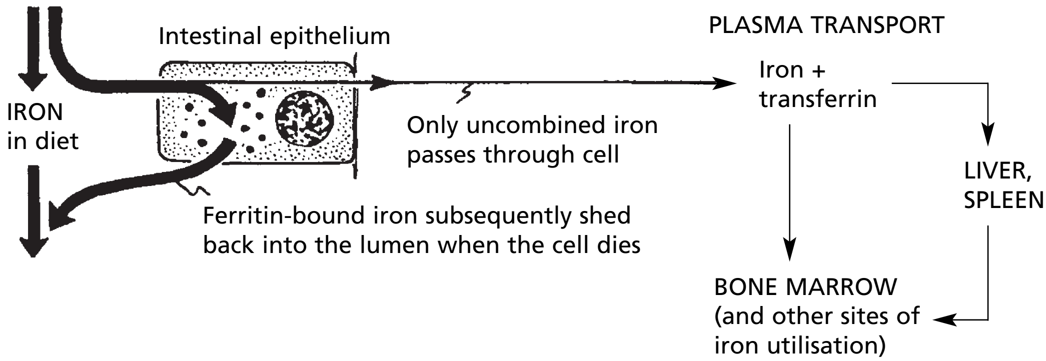


ENDOGENOUS PIGMENTATION

Haemosiderin *(continued)*

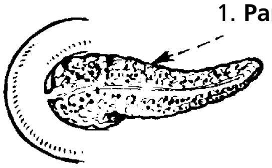
(b) *Haemochromatosis (Bronzed diabetes)*

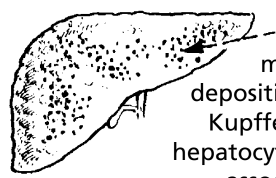
The absorption of iron from the intestine is controlled by the ferritin-transferrin mechanism.

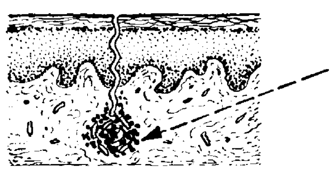


The ferritin content of the intestinal epithelium, iron saturation of the plasma, stores of iron in the liver and spleen and the demand for iron by the bone marrow form a balancing mechanism preventing overloading of any part of the system.

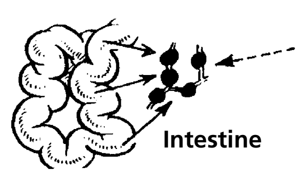
In haemochromatosis there is an inherited defect on chromosome 6 resulting in uncontrolled absorption of iron. The system becomes overloaded and iron is deposited as haemosiderin in many sites, the main ones being:











Haemosiderin may be found in almost any site in the body.

ENDOGENOUS PIGMENTATION

Haemoglobin

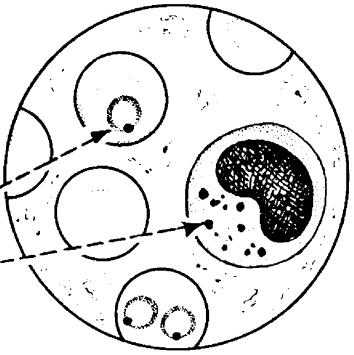
Intravascular haemolysis can result in haemoglobin appearing in the urine, giving it a dull red colour. In severe acute haemolysis (e.g. incompatible blood transfusion) acute renal tubular necrosis occurs. In chronic haemolysis (e.g. paroxysmal haemoglobinuria), some of the haemoglobin is reabsorbed and subsequently broken down so that iron, as haemosiderin, appears in the renal tubular epithelium.



(Demonstrated by the Prussian blue reaction)

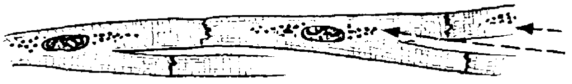
Haematin (or haemazoin)

This is a brown pigment produced by malarial parasites from haemoglobin. It is taken up by the monocytes in the blood and subsequently deposited in the liver and spleen.



Lipofuscin

This is a yellowish brown pigment with a high lipid content, often found in the atrophied cells of old age – 'wear and tear' pigment. It is particularly common in the heart muscle, and the term 'brown atrophy' is often applied.



It is also found in liver cells, testes and nerve cells.

EXOGENOUS PIGMENTATION – DEGENERATIONS

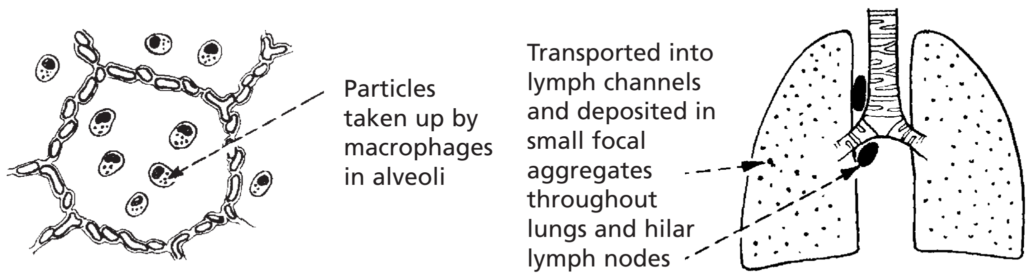
EXOGENOUS PIGMENTATION

Pigments may be introduced by inhalation, ingestion or injection.

Inhalation

The commonest substances inhaled are COAL DUST (carbon) – black, and STONE DUST (silica) – grey.

The particles reach the alveoli especially if the bronchial ciliary action is disturbed by chronic bronchitis.



The effects are described in detail under PNEUMOCONIOSIS.

Ingestion

Pigmentation can be caused by chronic ingestion of metals such as silver or lead. In both, the skin has a metallic hue, and in the case of lead a blue line appears on the gums due to interaction between lead and hydrogen sulphide. Excessive intake of carrots can lead to yellowish red skin pigmentation caused by carotene.

Injection

Tattooing is the most striking example of pigmentation following injection.

DEGENERATIONS

1. **Hyaline**

This is a descriptive term meaning a glossy, refractile appearance, seen in sections stained with haematoxylin and eosin. It is most commonly encountered in the form of dense collagen, particularly in benign tumours such as leiomyomas where the collagen has replaced muscle fibres, and in blood vessels in arteriosclerosis.

The term 'Mallory's hyaline' refers to an *intra*cellular accumulation of cytoskeletal proteins, e.g. in alcoholic liver disease (p.348).

2. **Mucoid**

This is a common change in epithelial tumours which secrete mucin. In these cases the epithelial cells undergo degeneration and appear to dissolve in the mucin.

Connective tissue may also accumulate mucin. Spaces filled with mucopolysaccharides (e.g. hyaluronic acid) appear between the fibres. The change is common in some tumours and the term 'myxomatous' may be used.

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CHAPTER 2

INFLAMMATION

INFLAMMATION

Inflammation is the dynamic process by which living tissues react to injury. They concern vascular and connective tissues particularly.

Causes:
Various agents may kill or damage cells:

PHYSICAL
- Trauma
- Heat or cold
- Radiation

CHEMICAL
- Simple chemical poisons, e.g. acids
- Organic poisons, e.g. paraquat

INFECTIVE
- Bacteria
- Viruses
- Parasites

IMMUNOLOGICAL
- Antigen-antibody
- Cell-mediated

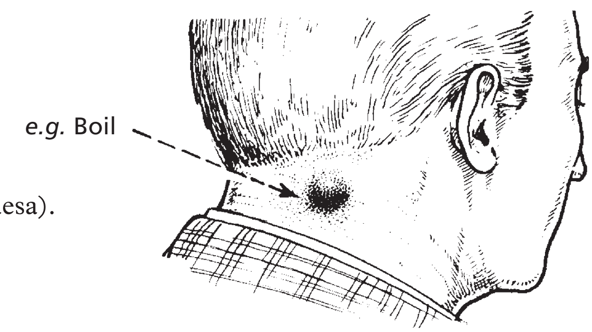
… and any other circumstance leading to tissue damage, e.g. VASCULAR or HORMONAL DISTURBANCE.

The inflammatory reaction takes place in the surviving adjacent vascular and connective tissues; the specialised parenchymal cells do not directly participate.

The initial stages are known as the **acute** inflammatory reaction. Where the process is prolonged the inflammation may be **subacute** or **chronic**.

ACUTE INFLAMMATION
The classical signs are:

REDNESS (rubor)
HEAT (calor)
SWELLING (tumour)
PAIN (dolor)
LOSS OF FUNCTION (functio laesa).



These gross signs are explained by changes occurring at microscopic level. Three essential features are:

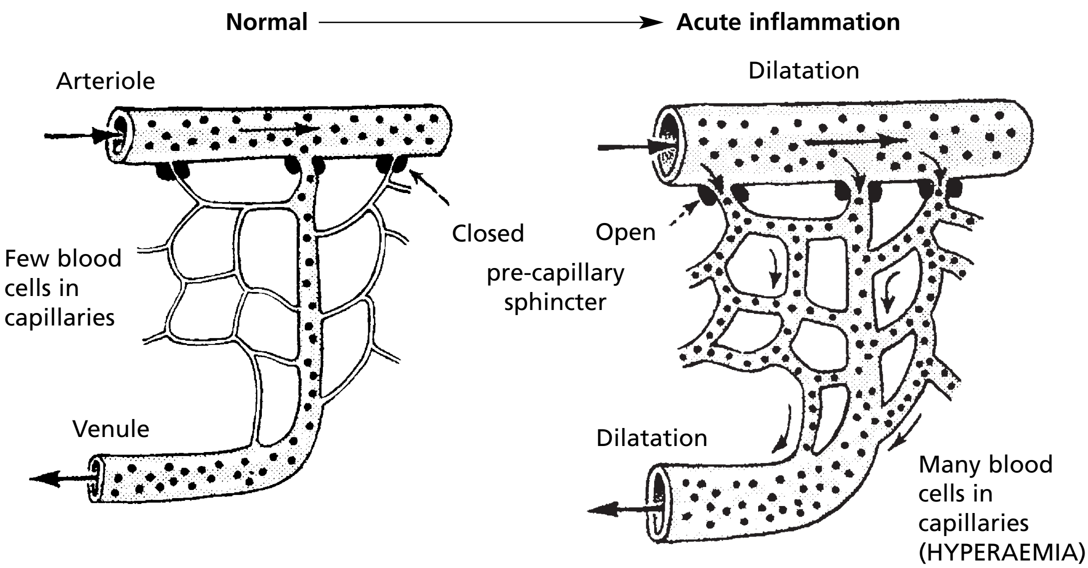
1. **HYPERAEMIA**
2. **EXUDATION OF FLUID**
3. **EMIGRATION OF LEUCOCYTES.**

ACUTE INFLAMMATION

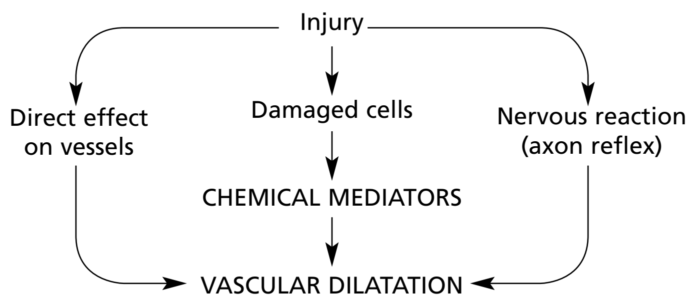
HYPERAEMIA

The hyperaemia in inflammation is associated with the well known microvascular changes which occur in Lewis' triple response – a FLUSH, a FLARE and a WEAL. It occurs when a blunt instrument is drawn firmly across the skin and illustrates the vascular changes occurring in acute inflammation.

The stroke is marked momentarily by a white line due to VASOCONSTRICTION.
The flush, a dull red line, immediately follows and is due to CAPILLARY DILATATION.
The flare, a bright red irregular surrounding zone, is due to ARTERIOLAR DILATATION.



Mechanisms involved are:



HYPERAEMIA explains the classical signs of REDNESS and HEAT.

ACUTE INFLAMMATION

EXUDATION

Exudation is the increased passage of protein-rich fluid through the vessel wall into the interstitial tissue. It explains the **weal** in Lewis' triple response.

Advantageous results

Fluid increase
↓
Dilution of toxins

Contents of fluid

(a) Globulins → protective antibodies
(b) Fibrin deposition → Helps to limit spread of bacteria
(c) Various factors promoting subsequent healing

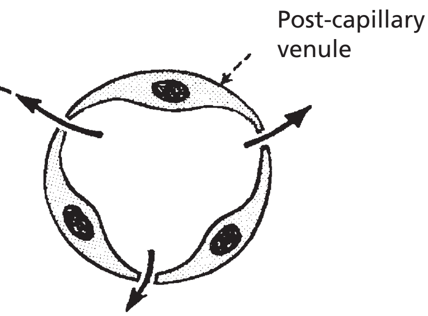
Mechanism

1. ***Protein passage***

Chemical mediators (e.g. histamine, bradykinin, leukotrienes) → Endothelial contraction – formation of gaps (rapid, short-lived, venules) → Increased permeability

Chemical mediators (e.g. histamine, bradykinin, leukotrienes) → Increased permeability

Direct endothelial injury (delayed, prolonged, all vessels), e.g. burns → Increased permeability



Leak of **proteins**, roughly in proportion to their molecular size: *albumin* (smallest) greatest in amount, but all plasma proteins present. If capillary damage is severe, FIBRINOGEN (largest molecule) escapes.

2. ***Fluid movement***

Hyperaemia → Capillary blood pressure rises → INCREASED FILTRATION PRESSURE

Loss of protein from capillaries → Reduced plasma osmotic pressure → INCREASED FILTRATION PRESSURE

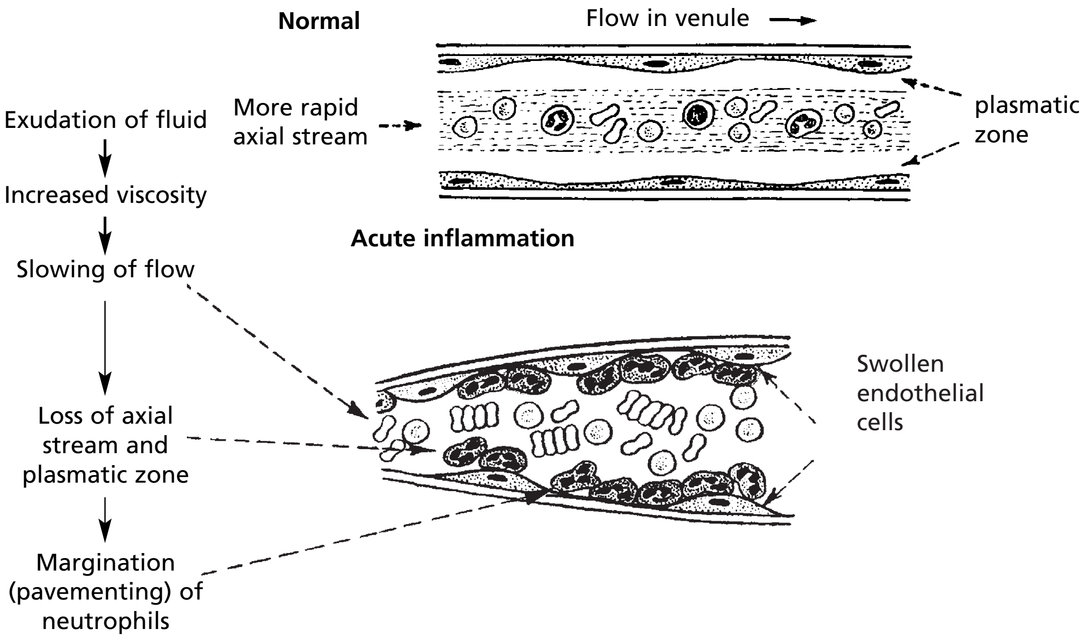
Interstitial tissue protein increase → Increased tissue osmotic pressure → INCREASED FILTRATION PRESSURE

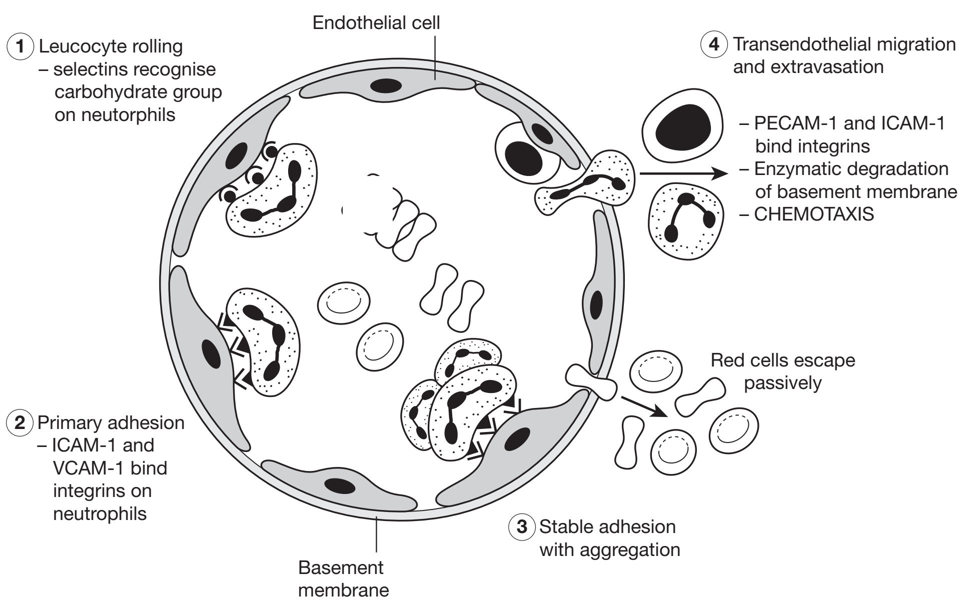
INCREASED FILTRATION PRESSURE
↓
Local swelling (OEDEMA) – 3rd classical sign
↓
Increased lymph flow from area

ACUTE INFLAMMATION

EMIGRATION OF LEUCOCYTES

Neutrophils and mononuclears pass between the endothelial cell junctions by amoeboid movement through the venule wall into the tissue spaces. In this process both neutrophils and endothelial cells are activated and both express cell adhesion molecules, initially SELECTINS and then INTEGRINS.



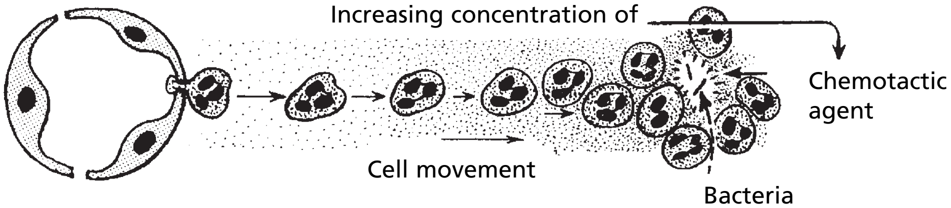


ACUTE INFLAMMATION

CHEMOTAXIS

The initial margination of neutrophils and mononuclears is potentiated by slowing of blood flow and by increased 'stickiness' of the endothelial surface.

After penetration of the vessel wall, the subsequent movement of the leucocytes is controlled by CHEMOTAXIS. The cell moves in response to an increasing concentration gradient of the particular chemotactic agent, usually a protein or polypeptide.



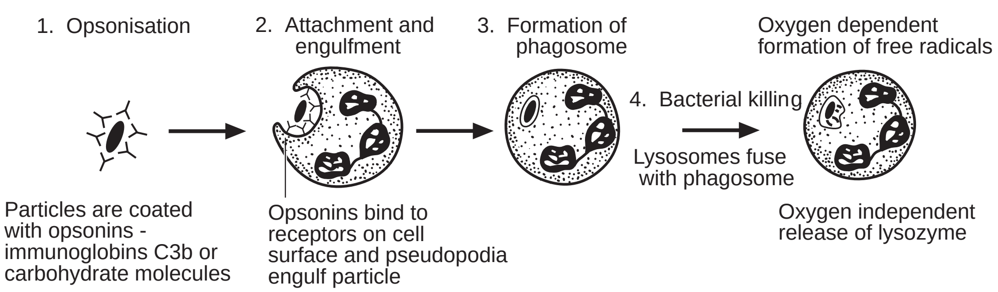
Important examples of chemotactic agents are:

Fractions of the COMPLEMENT SYSTEM (esp. C3a)
Factors derived from arachidonic acid by the neutrophils – LEUKOTRIENES (e.g. LTB4)
Factors derived from pathogenic BACTERIA
Factors derived from sensitised lymphocytes – CYTOKINES (e.g. IL-8).

The leucocytes move by extension of an anterior pseudopod with attachment to extracellular matrix molecules such as fibronectin using cell adhesion molecules. The cell body is then pulled forward by actin and myosin filaments.

PHAGOCYTOSIS

This is the process by which neutrophils and macrophages clear the injurious agent. It is an important defence mechanism in bacterial infections particularly.



There are 3 families of OPSONIN.

1. Immunoglobulin, especially IgG
   – recognized by Fc receptors on neutrophil surface.
2. Complement, especially C3b
   – recognized by C3b receptors on neutrophil surface.
3. Carbohydrate binding proteins, or lectins
   – bind sugar residues on bacterial cell walls.

The opsonic activity is enhanced when it is confined within a solid organ or rigid medium such as a fibrin network; where conditions are looser and more fluid, activity is diminished.

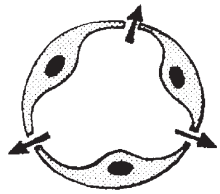
ACUTE INFLAMMATION

CHEMICAL MEDIATORS

Various chemical mediators have roles in the inflammatory process. They may be circulating in plasma and require activation or they may be secreted by inflammatory cells. Many of these mediators have overlapping actions.

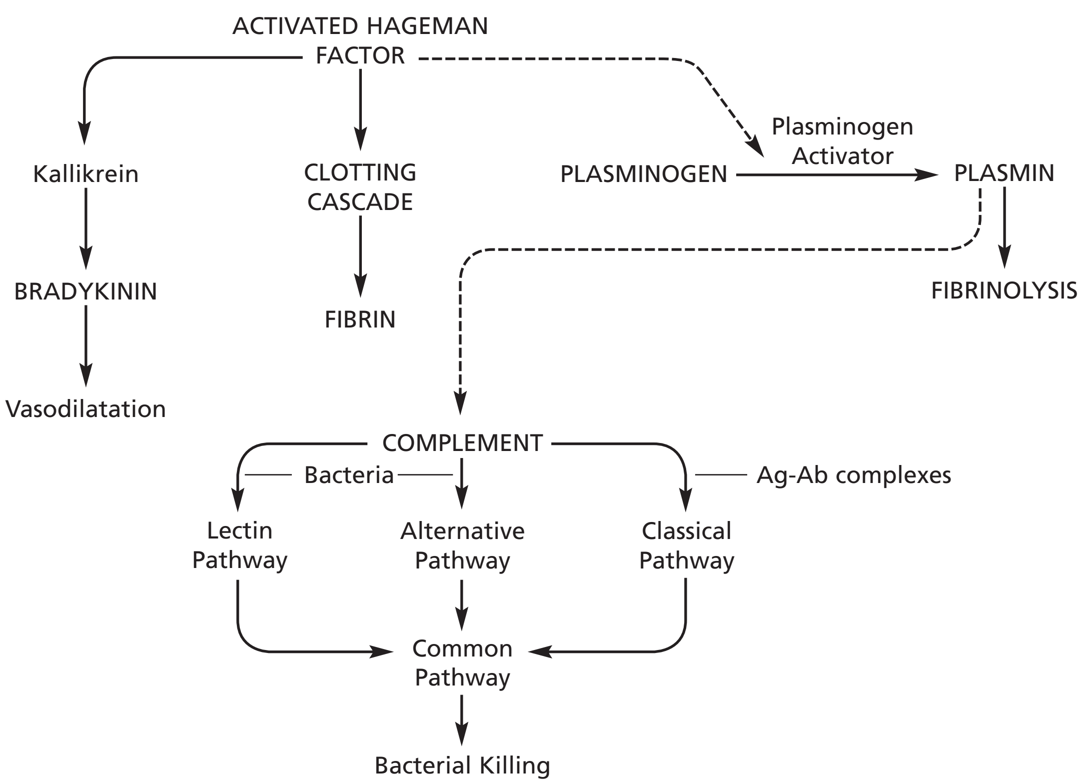
Mediators dervived from:

1. Inflammatory cells

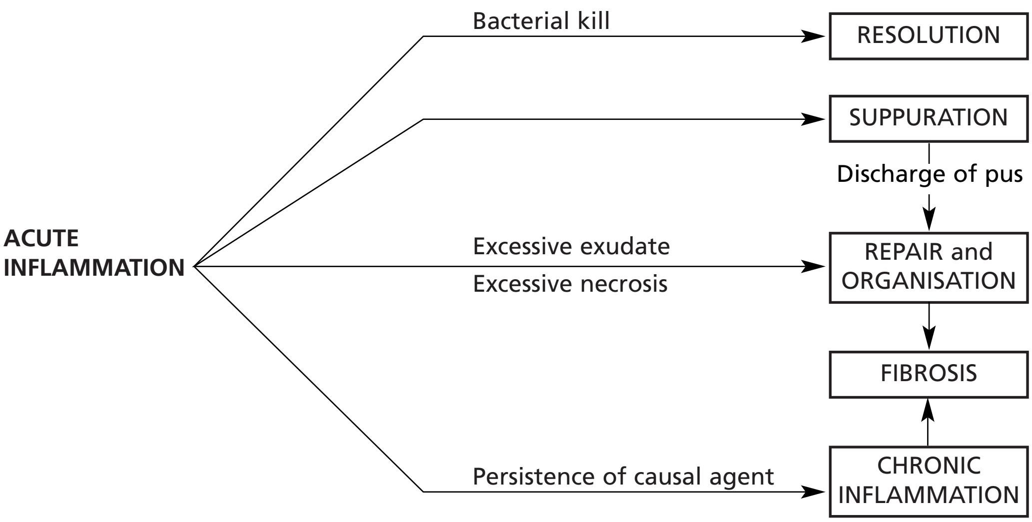


- Histamine (Mast cells) → Increased vascular permeability
- Histamine (Mast cells) → Vasodilatation
- Serotonin (Platelets) ⇢ Vasodilatation
- Arachidonic Acid Derivatives → Prostaglandins → Vasodilatation, oedema (PGE_2, PGI_2)
- Arachidonic Acid Derivatives → Leukotrienes → Vasoconstriction; increased permeability
- Cytokines (inflammatory cells, endothelium etc.) → IL-2, IL-4 → Stimulate lymphocyte proliferation
- Cytokines (inflammatory cells, endothelium etc.) → IL-10, TGF-β → Suppress lymphocyte proliferation
- Cytokines (inflammatory cells, endothelium etc.) → IFN-γ, TNF-α → Macrophage activation

2. Plasma. These pathways are all interrelated.



SEQUELS OF ACUTE INFLAMMATION

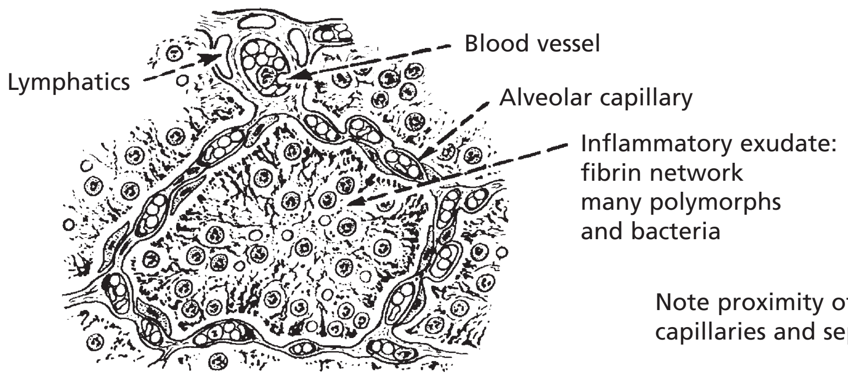


RESOLUTION

This means the complete restoration of normal conditions after the acute inflammation. The three main features which potentiate this sequel are:

1. minimal cell death and tissue damage
2. rapid elimination of the causal agent, e.g. bacteria
3. local conditions favouring removal of fluid and debris.

Resolution of lobar pneumonia (bacterial inflammation of lung alveoli) is a good example:



Note proximity of exudate to alveolar capillaries and septal lymphatics.

Following bacterial kill the mechanism is as follows:

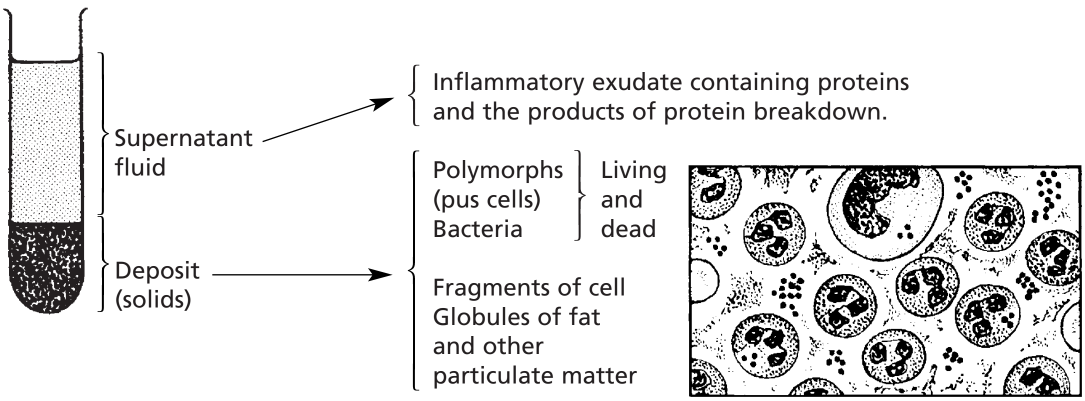
1. Solution of fibrin by enzyme action (polymorphs and fibrinolysin)
2. Removal of fluid by blood vessels and lymphatics
3. Removal of all debris by phagocytes to hilar lymph nodes
4. The capillary hyperaemia diminishes and restoration to normal is complete.

SEQUELS OF ACUTE INFLAMMATION

SUPPURATION

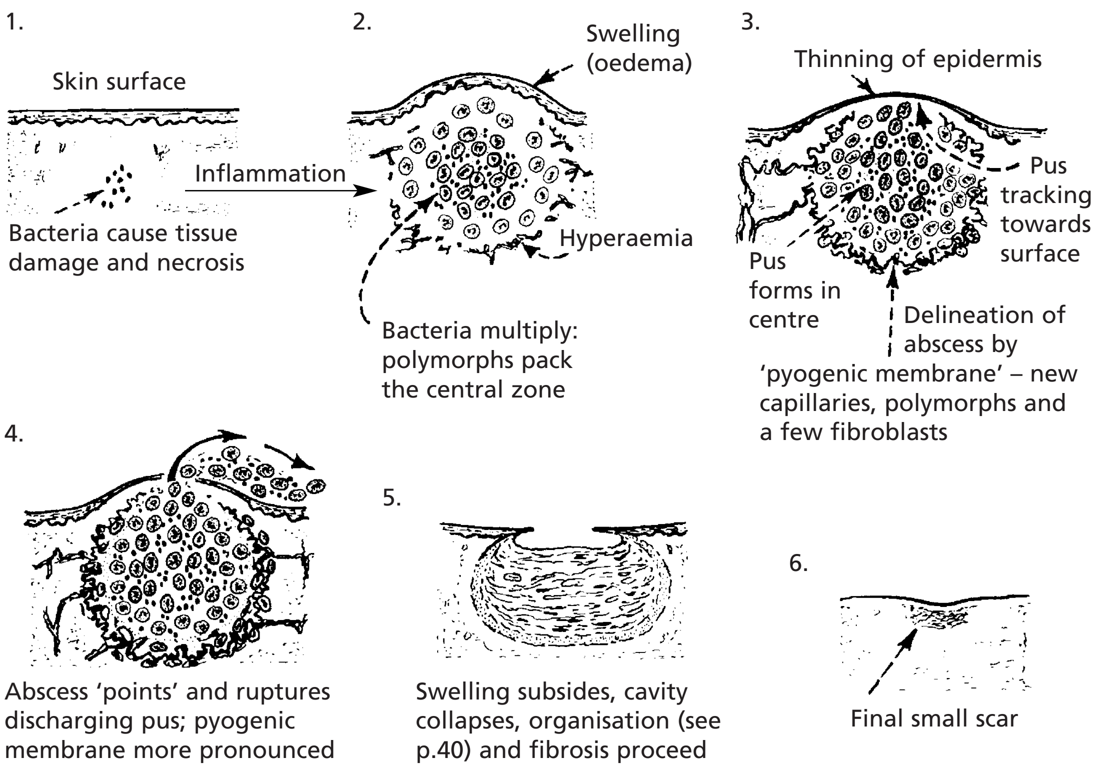
This means the formation of PUS; where pus accumulates an ABSCESS forms.

Infection by pyogenic (pus-forming) bacteria is the usual cause, e.g. staphylococcal abscess (or boil). The pus in this case is a thick, creamy yellow fluid which, on centrifugation, separates thus:



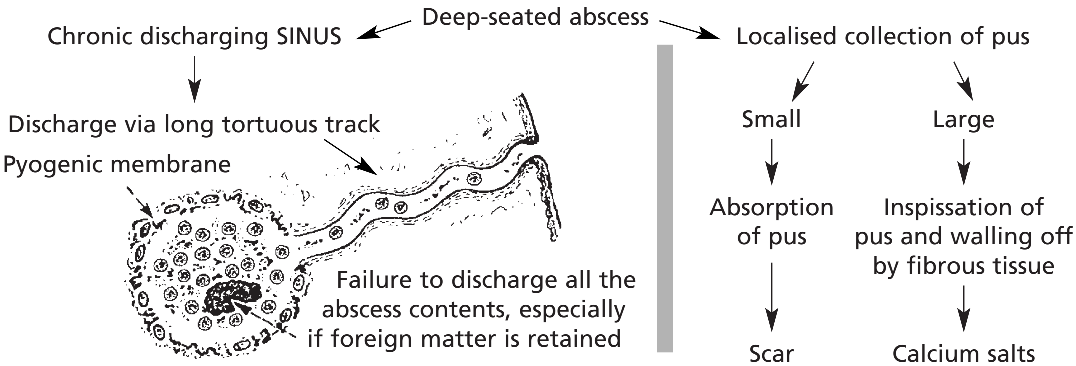
Evolution of an abscess

The usual evolution of an abscess is as follows:



SEQUELS OF ACUTE INFLAMMATION

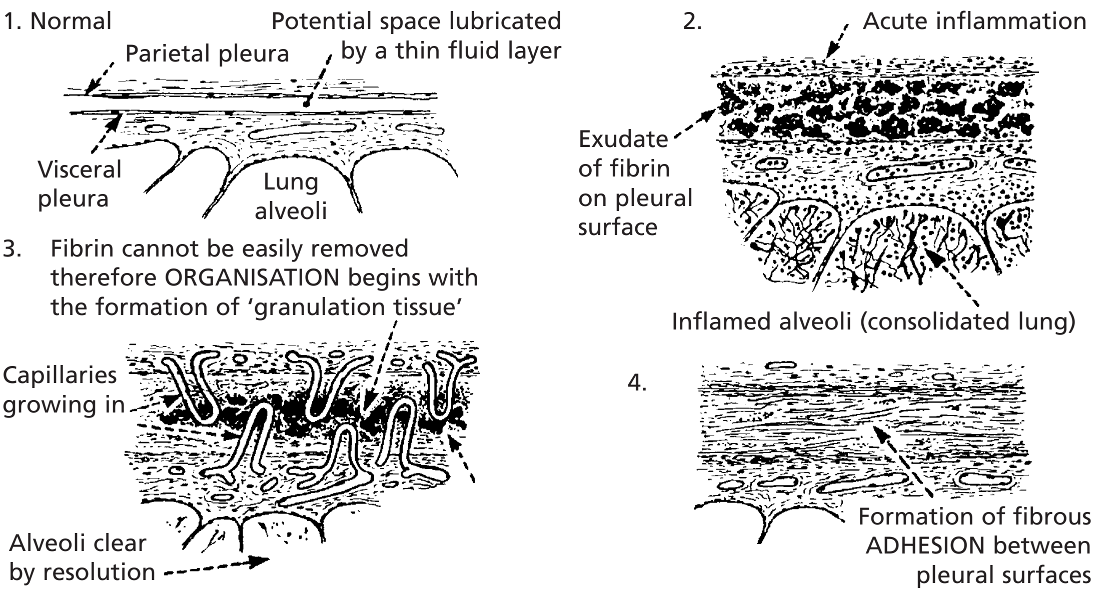
Evolution of an abscess *(continued)*
When the abscess is deep-seated, the process may be modified as follows:



ORGANISATION AND FIBROSIS
Organisation occurs when, during the acute inflammatory process, (a) there is excessive exudation or necrosis or (b) when local conditions are unfavourable for the removal of exudate and debris. The term also applies to the local reaction to the presence of thrombus and also the necrosis associated with infarction.

The changes are similar to those described in wound healing viz – the growth of new capillaries into the inert material (exudate or thrombus), the migration of macrophages and the proliferation of fibroblasts resulting in FIBROSIS.

A good example of organisation following acute inflammation is seen in the pleura overlying pneumonia. The inflammation of the lung tissue proper usually resolves completely (p.264); in contrast the pleural exudate is not easily removed and organisation takes place.



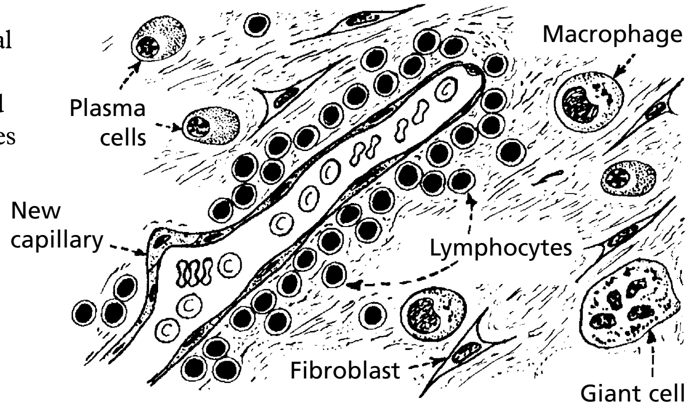
Other good examples of organisation are seen after infarction (see p.166).

CHRONIC INFLAMMATION

Chronic Inflammation may (a) follow acute inflammation if the causal agent is not removed: or (b) be 'primary', i.e. there is no pre-existing acute stage.

The essential changes are:

1. Absence of polymorphs (natural life span of 1–3 days); the appearance of lymphocytes and often plasma cells. Macrophages play an increasingly important role including removing dead polymorphs, presentation of antigenic material and granuloma formation.
2. Proliferation of vascular endothelium by 'budding' – formation of new capillaries (angiogenesis).
3. Proliferation of fibroblasts with collagen production leading to
4. Fibrosis.

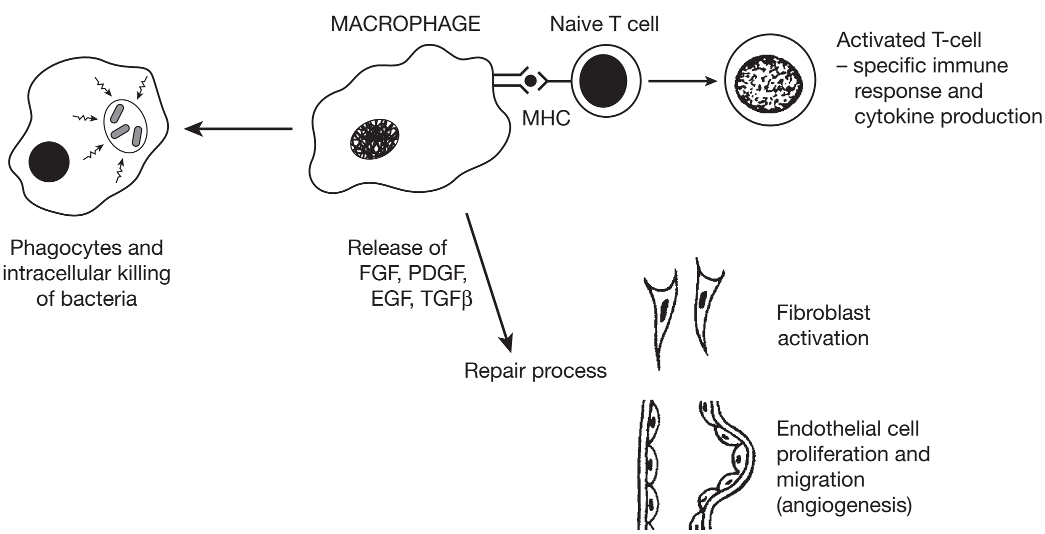


Common causes of 'primary' chronic inflammation include:

(a) Persistent infections, e.g. tuberculosis, leprosy – where the organisms are resistant to neutrophil attack and bacteria survive within macrophages.
(b) Foreign material, e.g. silicates, including asbestos.
(c) Auto-immune diseases, e.g. auto-immune thyroiditis.
(d) Conditions of unknown aetiology, e.g. sarcoidosis: Crohn's disease.

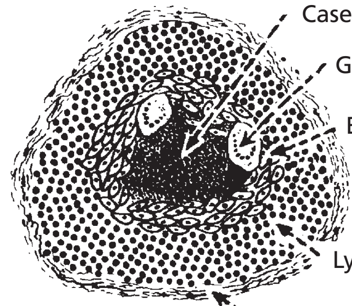
Cellular interactions

The macrophage is the key cell that directs the various cells involved in chronic inflammation.



CHRONIC INFLAMMATION

GRANULOMATOUS INFLAMMATION
This is the term given to forms of chronic inflammation in which modified macrophages (epithelioid cells) accumulate in small clusters surrounded by lymphocytes. The small clusters are called GRANULOMAS. The basic lesion in TUBERCULOSIS is a good example.



Similar granulomas are seen in:

Sarcoidosis – a rare inflammatory disease of unknown aetiology affecting especially the lymph nodes and lungs, but also many other organs.

'Talc' granuloma – where particulate silicates introduced into the tissues evoke an inflammatory reaction after a latent period (usually years).

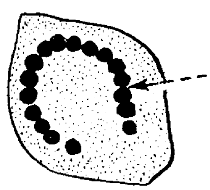
Crohn's disease – a chronic inflammatory disease affecting the terminal ileum and colon (see p.309).

Lymph nodes draining ulcerated areas in which breakdown of lipid is occurring.

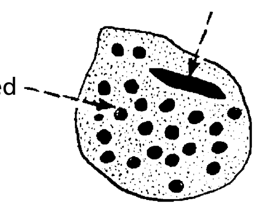
N.B. In all of these granulomatous diseases the basic lesion may be identical, but CASEATION only occurs in tuberculosis.

The epithelioid cells of the granulomas are modified macrophages, and giant cells are derived from macrophages usually by cell fusion but occasionally by nuclear division without cytoplasmic separation.

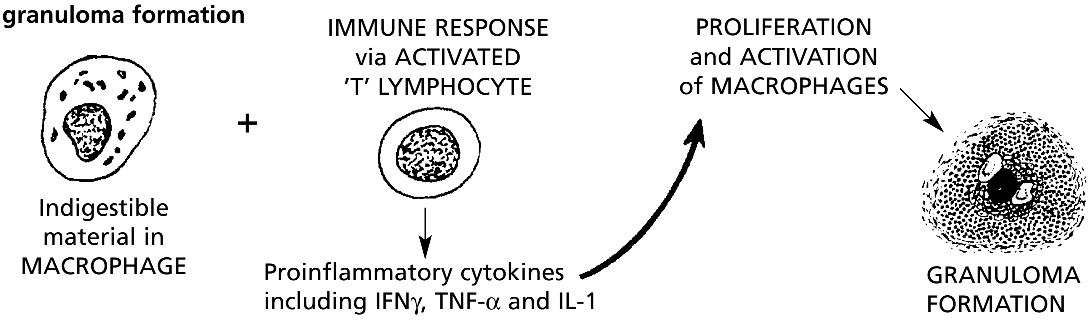
The Langhans' giant cell – seen in chronic granulomata, e.g. tuberculosis and sarcoidosis.



The foreign body giant cell – seen in association with particulate insoluble material.



Mechanism of granuloma formation



ULCERATION – BENIGN

ULCERATION is a complication of many disease processes.

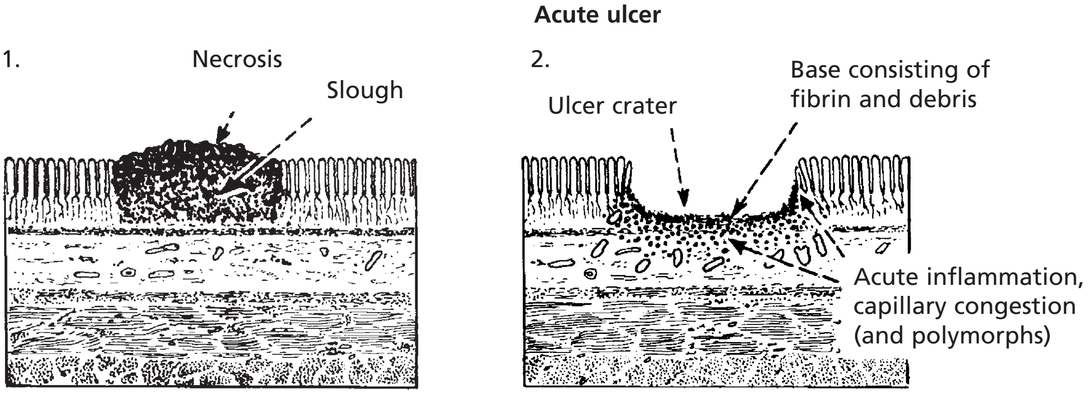
An **ulcer** is formed when the surface covering of an organ or tissue is lost due to necrosis and replaced by inflammatory tissue.

The most common sites are the alimentary tract and the skin.

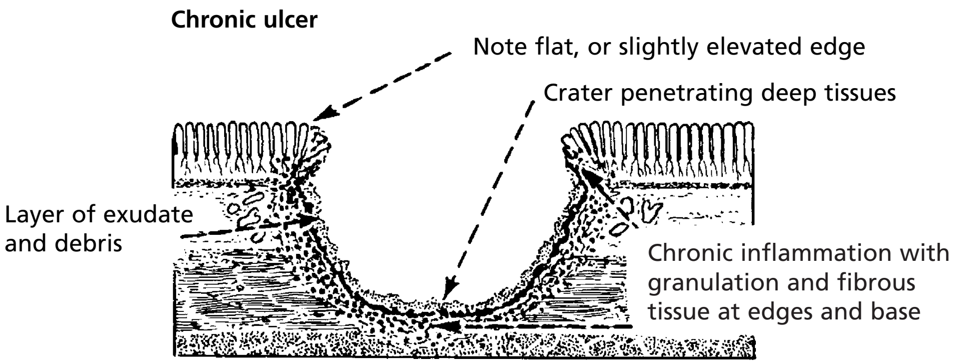
Ulcers are divided into two main groups: 1. BENIGN (inflammatory) and 2. MALIGNANT (cancerous).

The word 'benign' is used here in the limited sense of contrasting with 'malignant': 'benign' ulcers may have serious consequences.

Evolution of a benign ulcer



Healing can occur at this stage with restoration to normal, but if irritation (e.g. bacterial action, slight trauma, digestive juices and acid) continues, a CHRONIC ULCER forms.

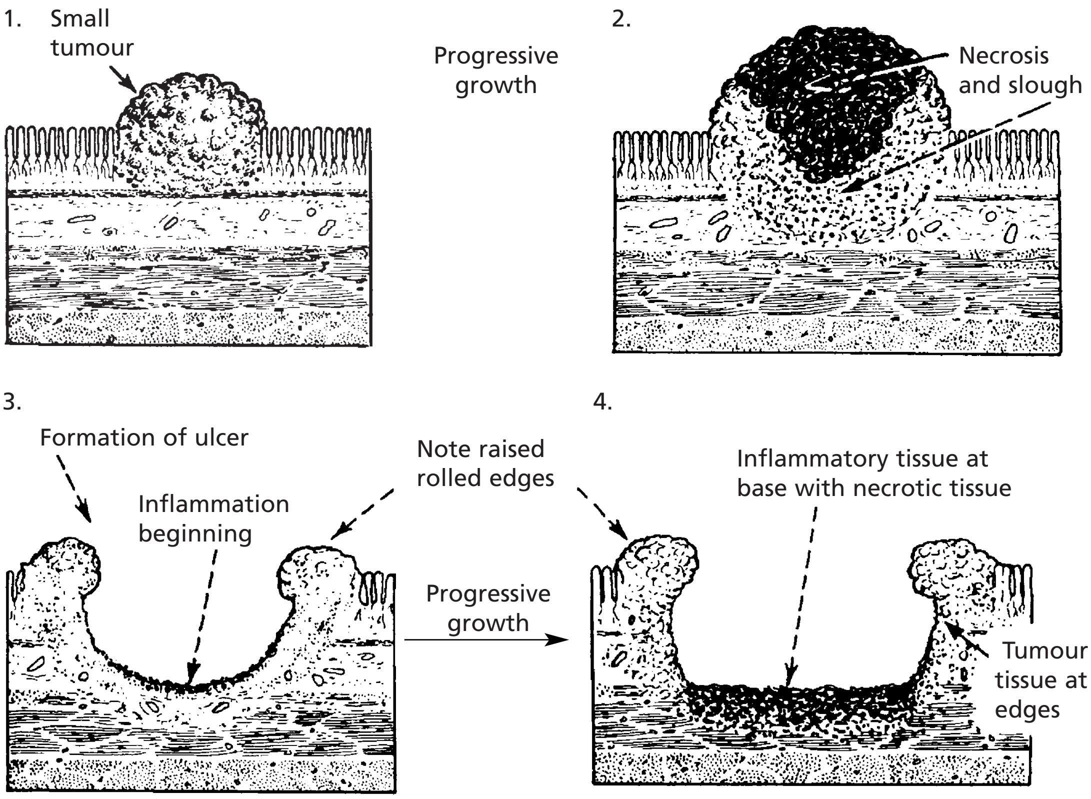


Healing of a chronic ulcer may be impeded by the secondary obliterative changes in the blood vessels due to the chronic inflammation, and it is inevitably associated with a variable amount of scarring.

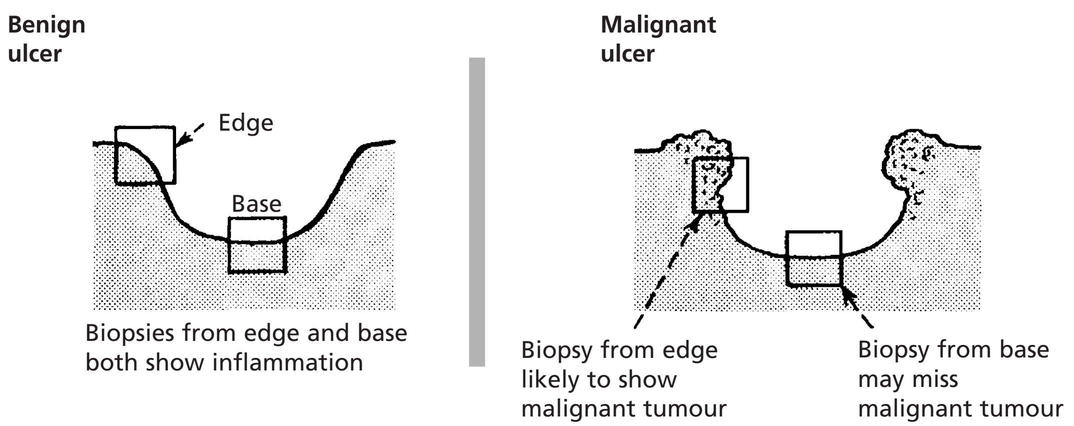
ULCERATION – MALIGNANT

Evolution of a malignant ulcer (ulcerated tumour)

Such an ulcer is the result of the growth of a malignant tumour.



The differences between benign and malignant ulcers are most prominent at the edges – from which a diagnostic biopsy should be taken. It is worth remembering that cancers often ulcerate but benign ulcers rarely undergo malignant change.



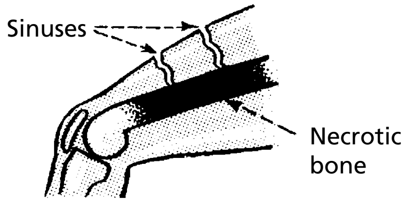
INFLAMMATION – ANATOMICAL VARIETIES

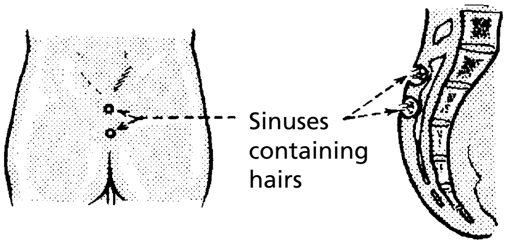
SINUS

A sinus is a tract lined usually by granulation tissue leading from a chronically inflamed cavity to a surface. In many cases the cause is the continuing presence of 'foreign' or necrotic material.

Examples include:

- **Sinuses associated with osteomyelitis** (inflammation of bone).
  Where necrosis of bone occurs, chronic sinuses form over it.
- **Pilonidal sinus** (pilonidal = nest of hairs).
  Seen in the mid-line over the sacrum (natal cleft) where hairs which have penetrated deeply under the skin are associated with chronic relapsing inflammation.





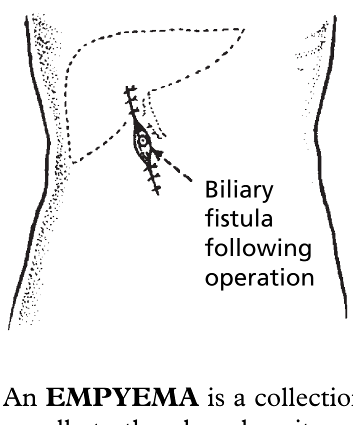
FISTULA

A fistula is a track open at both ends, through which abnormal communication between two surfaces is established.

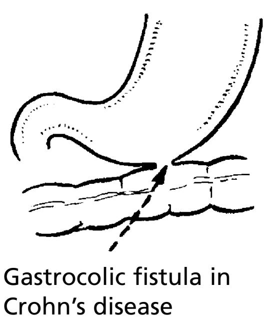
There are two main types:

1. **Congenital** – due to developmental abnormality: any inflammation is superimposed, e.g. tracheoesophageal fistula which can lead to choking and coughing during feeding in a newborn.
2. **Acquired** – due to:

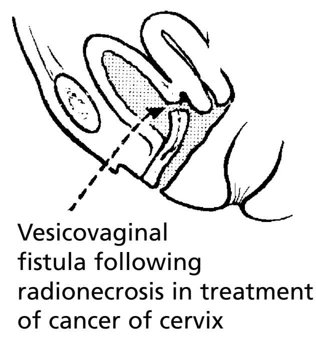
(a) Trauma



(b) Inflammation



(c) Necrosis – particularly of tumour



An **EMPYEMA** is a collection of pus in a body cavity or hollow organ. The term refers usually to the pleural cavity or the gall bladder.

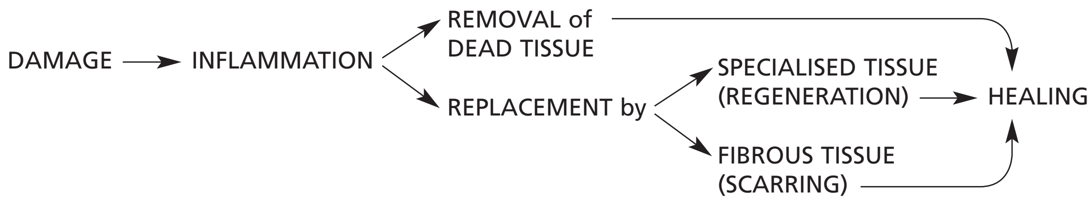
CELLULITIS occurs when inflammation spreads in the connective tissue planes.

CHAPTER 3

HEALING

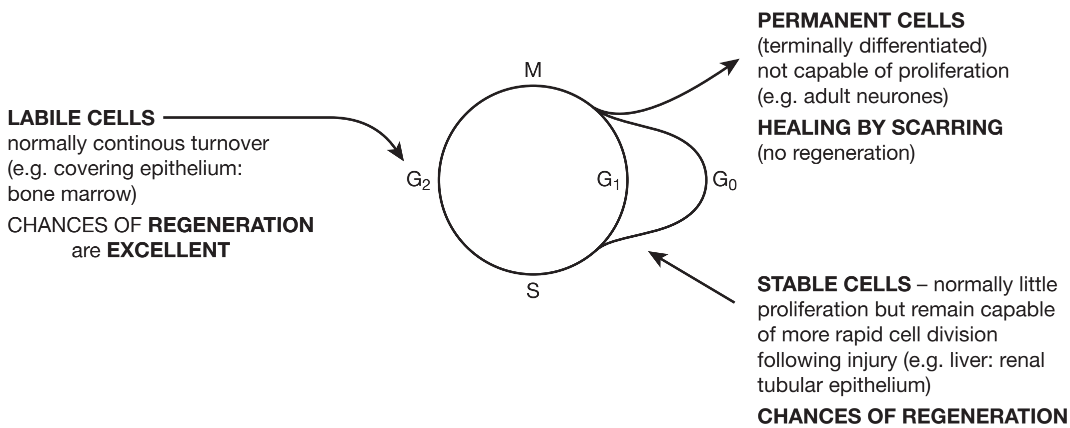
HEALING

Healing is the final stage of the response of tissue to injury.



The capacity of a tissue for REGENERATION depends on its PROLIFERATIVE ABILITY and on the type and severity of the damage. In particular, regeneration is not possible if the STEM CELLS are destroyed.

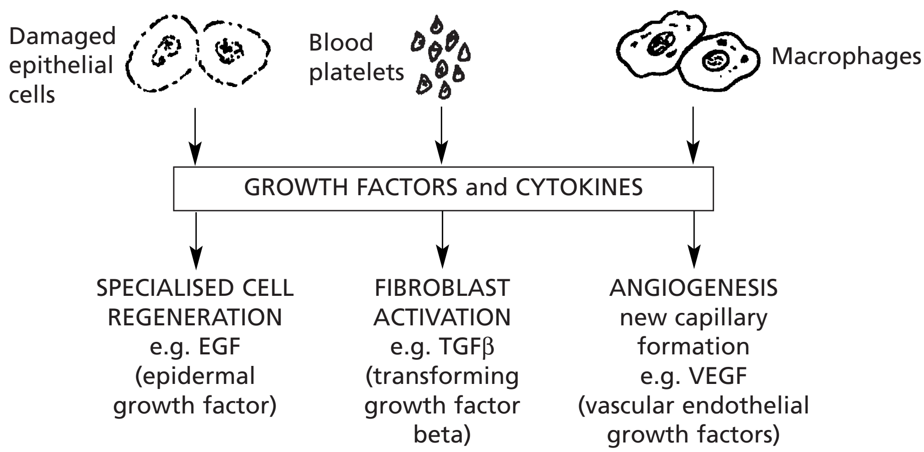
Three broad GROUPS of cells are considered in the context of the cell cycle (p.3).



REGENERATION involves TWO PROCESSES:

1. PROLIFERATION of SURVIVING CELLS to replace lost tissue.
2. MIGRATION of SURVIVING CELLS into the vacant space.

The FACTORS which CONTROL healing and repair are complex: they include the production of a large variety of **growth factors.**

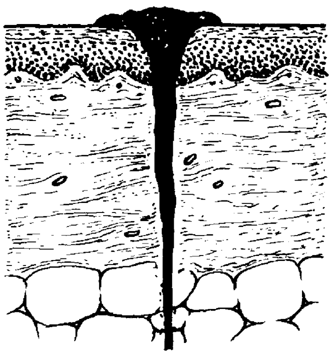


WOUND HEALING

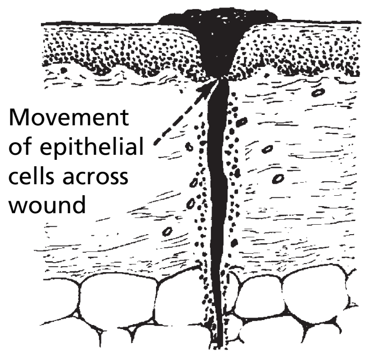
Healing of a wound shows both epithelial regeneration (healing of the epidermis) and repair by scarring (healing of the dermis).

Two patterns are described depending on the amount of tissue damage. These are the same process varying only in amount.

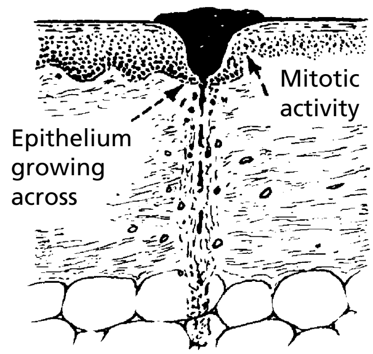
1. Healing by first intention (primary union)
This occurs in clean, incised wounds with good apposition of the edges – particularly planned surgical incisions.



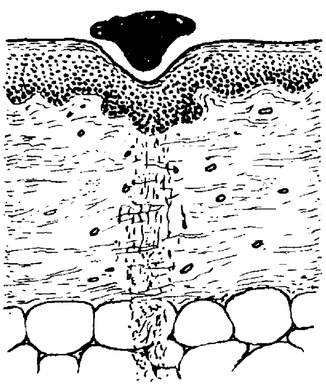
Immediately: Blood clot and debris fill the small cleft.



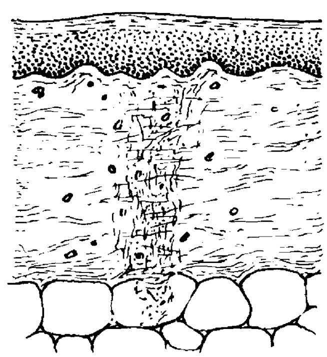
2–3 hours: Early inflammation close to edges. Mild hyperaemia and a few polymorphs.



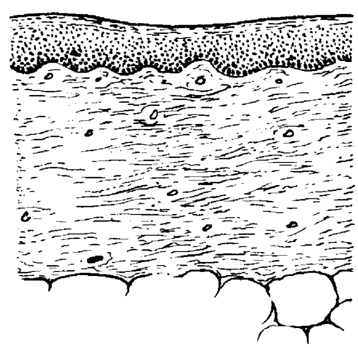
2–3 days: Macrophage activity removing clot. Proliferation of blood vessels.
Fibroblastic activity.



10–14 days: Scab loose and epithelial covering complete. Fibrous union of edges, but wound is still weak.



Weeks: Scar tissue still slightly hyperaemic.
Good fibrous union, but not full strength.



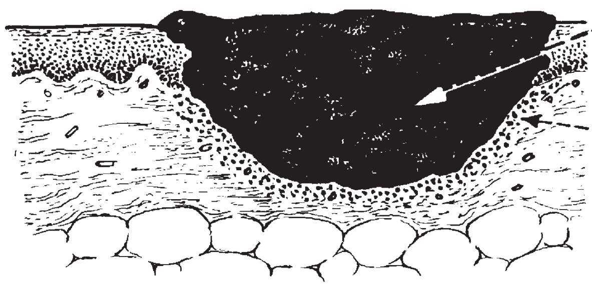
Months – years:
Devascularisation. Remodelling of collagen by enzyme action. Scar is now minimal and merges with surrounding tissues.

WOUND HEALING

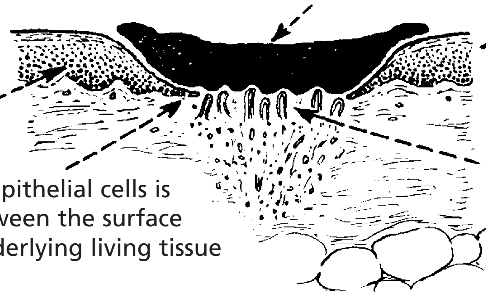
2. Healing by second intention (secondary union)

This occurs in open wounds, particularly when there has been significant loss of tissue, necrosis or infection.

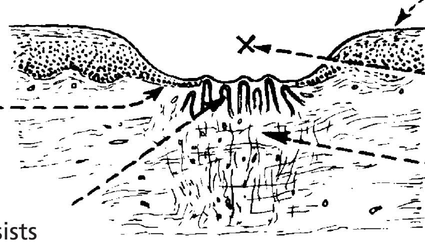
Early



A few days

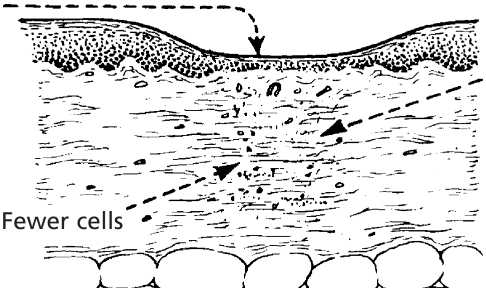


1 week approximately



Granulation tissue is seen in the base of the wound. This tissue consists of newly formed capillaries with fibroblasts and macrophages and occurs in many circumstances in addition to wounds.

2 weeks onwards



WOUND HEALING

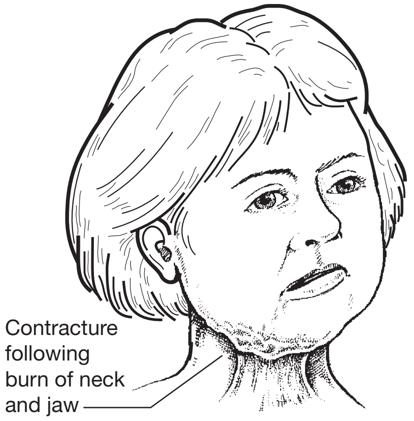
Wound contraction

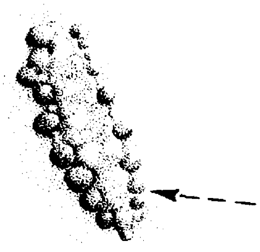
Wound contraction, which is beneficial and begins early, is due mainly to the young, specialised 'myofibroblasts' in the granulation tissue exerting a traction effect at the wound edges. The exposed surface is reduced by gradual regeneration of the surface epithelium. The remodelling of the collagen continues for many months.

COMPLICATIONS

1. Contracture

Later, CONTRACTURE may cause serious cosmetic and functional disability, particularly in deep and extensive skin burns and around joints if muscles are badly damaged.





2. Keloid

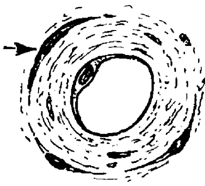
The formation of excess collagen in the form of thick interlacing bundles which causes marked swelling at the site of the wound is known as a KELOID. The essential cause is unknown. It is particularly common in black people.

HEALING – FIBROSIS

FIBROSIS is the end result of WOUND HEALING, CHRONIC INFLAMMATION and ORGANISATION.

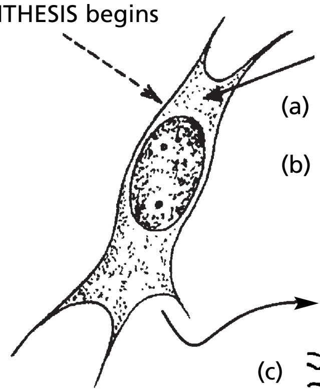
Formation of fibrous tissue

FIBROCYTES (and primitive stem cells) situated around capillaries and loose connective tissues



STIMULUS – growth factor, e.g. TGFβ (see p.48), derived from damaged cells and macrophages.

Enlarge to become active FIBROBLASTS and active PROTEIN SYNTHESIS begins



1. INTRACELLULAR PRODUCTION of COLLAGEN precursors.
   (a) Hydroxylation of proline and lysine (vit C required)
   (b) Triple helix formation.

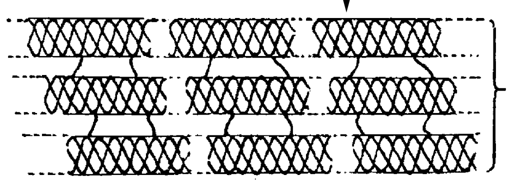


Secretion to EXTRACELLULAR SITE

2. Adhesive glyco-proteins – FIBRONECTINS which provide a scaffolding and contribute to the progress of the repair process

(c)  cleavage of terminal peptides

(d) Cross-linking + polymerisation



COLLAGEN FIBRE

REMODELLING follows: Action of COLLAGENASE ⟶ SCAR TISSUE
+ secretion of COLLAGEN

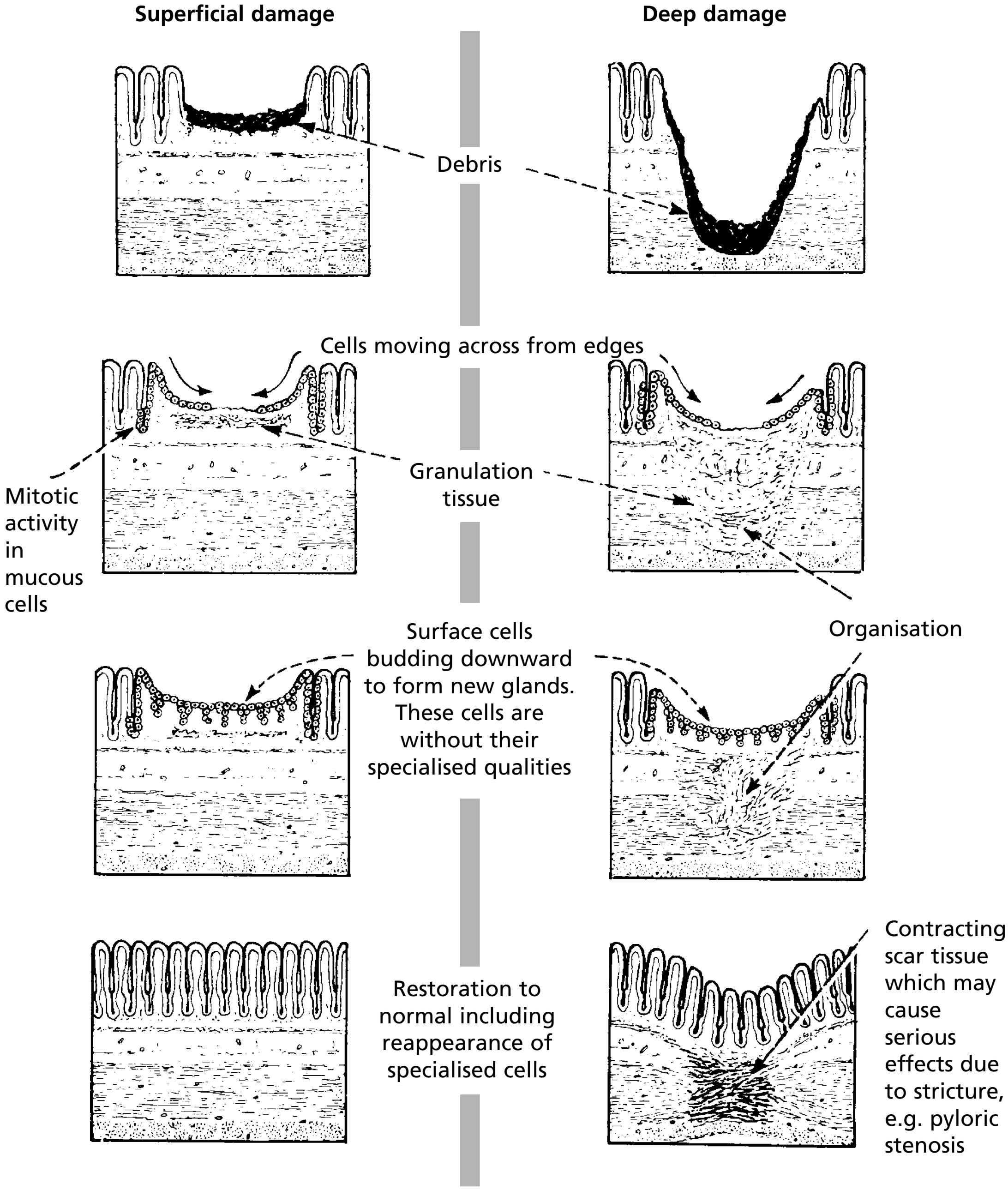
Factors delaying healing

1. Local
   INFECTION, a POOR BLOOD SUPPLY, excessive movement and presence of foreign material DELAY HEALING.
2. General
   DEFICIENCY of VITAMIN C
   DEFICIENCY of AMINO ACIDS (in malnutrition)
   DEFICIENCY of ZINC
   EXCESS of ADRENAL GLUCOCORTICOIDS
   DEBILITATING CHRONIC DISEASE
   } Failure of proper collagen synthesis with delayed healing and weak scars.

HEALING – SPECIAL SITUATIONS

INTERNAL SURFACES

The epithelial lining of the gastrointestinal tract regenerates in a similar way to the skin.

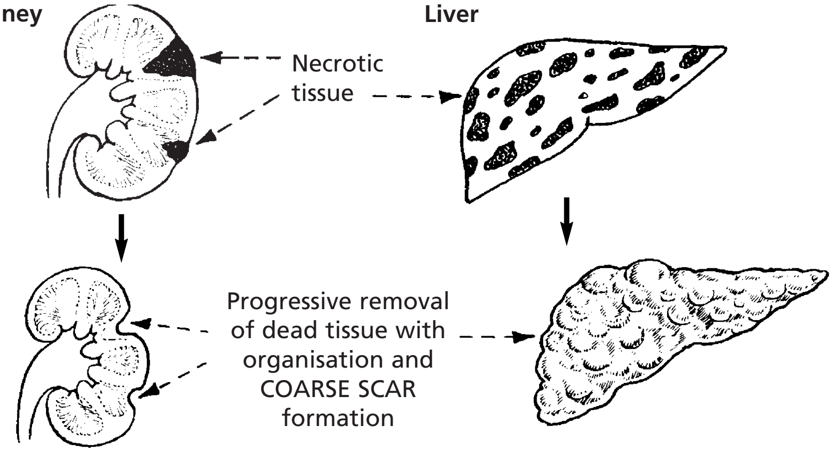


HEALING – SPECIAL SITUATIONS

SOLID EPITHELIAL ORGANS

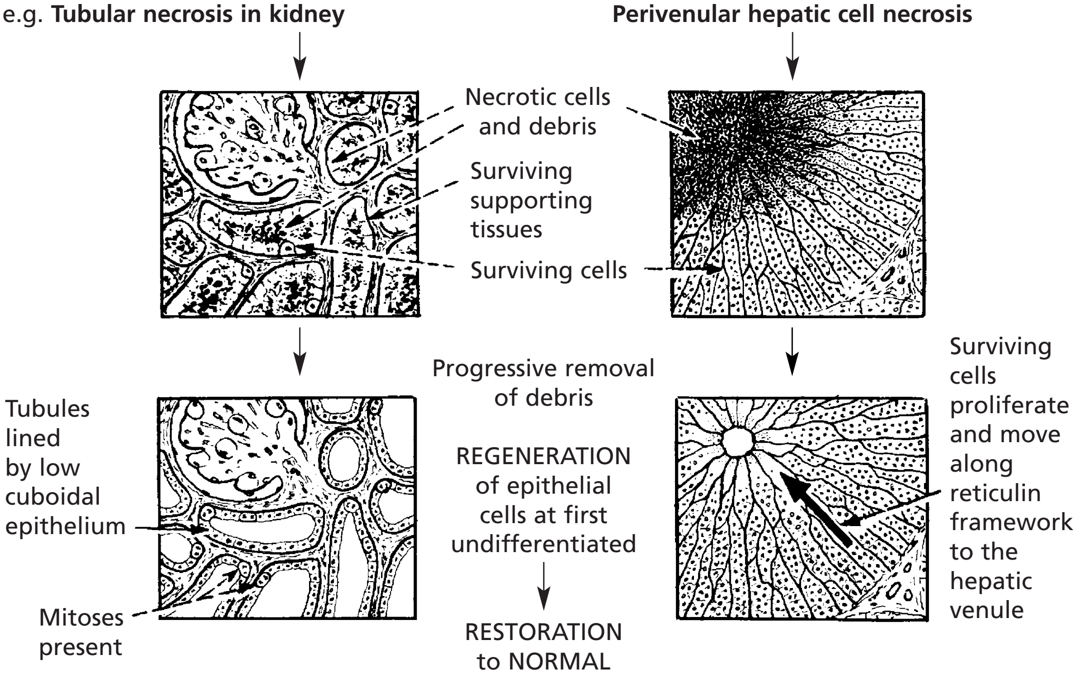
1. **Following gross tissue damage – including supporting tissue** (post-necrotic scarring)

e.g. **Kidney** **Liver**



2. **Following cell damage with survival of the supporting (reticular) tissues**

e.g. **Tubular necrosis in kidney** **Perivenular hepatic cell necrosis**



HEALING – SPECIAL SITUATIONS

MUSCLE

Muscle fibres of all 3 types – skeletal, cardiac and smooth – have only limited capacity to regenerate.

When a MASS of muscle tissue is damaged, repair by SCARRING occurs. This is particularly important in the HEART after infarction.

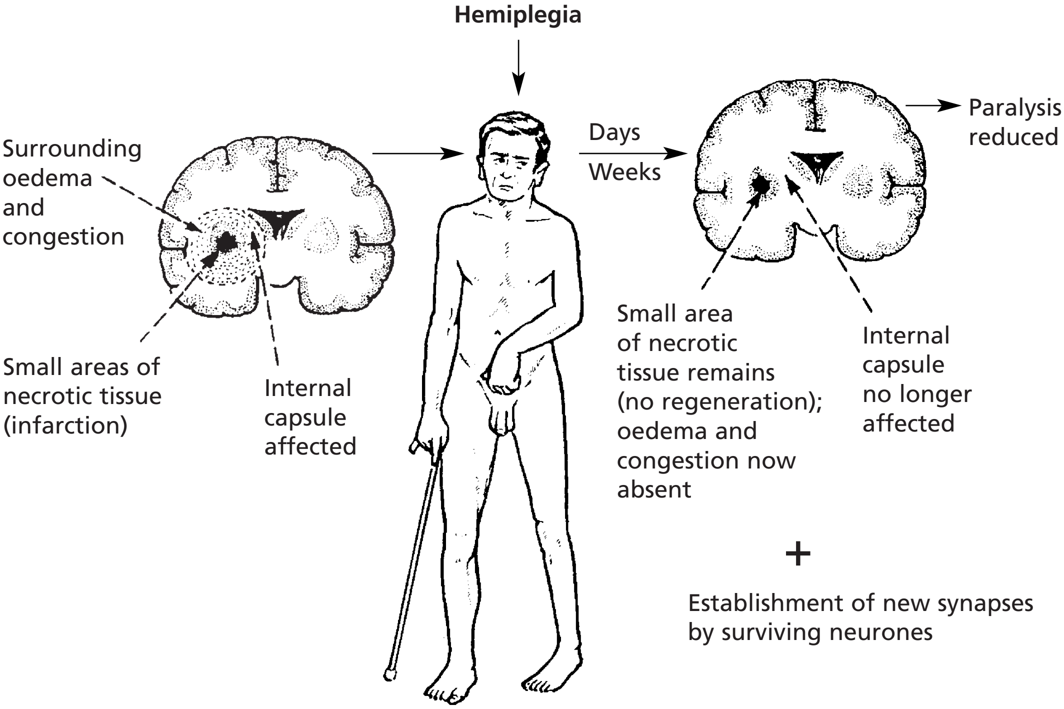
If the damage affects individual muscle fibres diffusely and with varying severity, then regeneration of the specialised fibres is possible (e.g. the myocardium may recover completely from the effects of diphtheria toxin and virus infection).

NERVOUS TISSUE

Central nervous system

Regeneration does not occur when a neurone is lost.

In cases of acute damage, the initial functional loss often exceeds the loss of actual nerve tissue because of the reactive changes in the surrounding tissue. As these changes diminish, some function may be restored.



Scarring within the CNS is by proliferation of ASTROCYTES and the production of fibrillary glial acidic protein – a process known as GLIOSIS.

HEALING – SPECIAL SITUATIONS

NERVOUS TISSUE *(continued)*

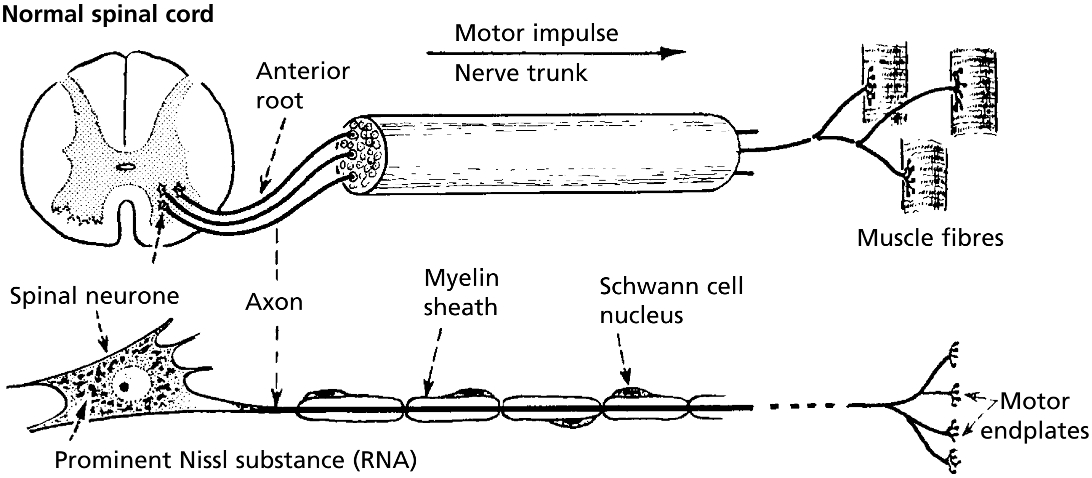
Peripheral Nerves

When a peripheral nerve is damaged, the axon and its myelin sheath rapidly degenerate distally. The supporting tissues of the nerve (Schwann cells) degenerate slowly.

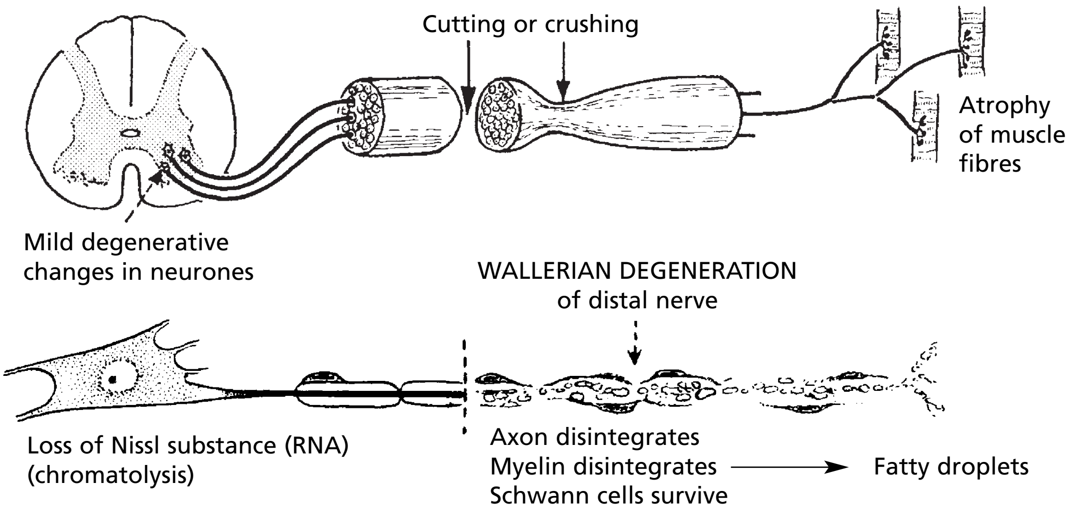
Regeneration can occur because the central neurone of which the axon is a peripheral extension is remote from the site of damage.

A spinal motor nerve is taken as an example.

Normal spinal cord



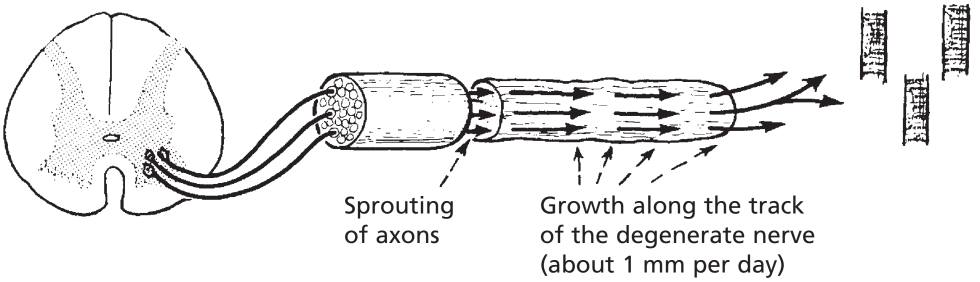
Results of damage



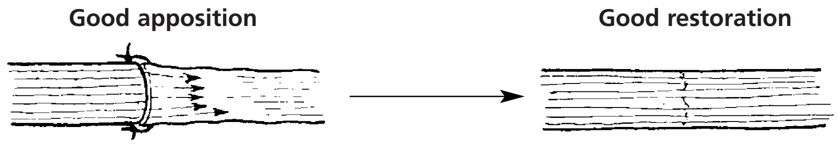
HEALING – SPECIAL SITUATIONS

Peripheral Nerves *(continued)*

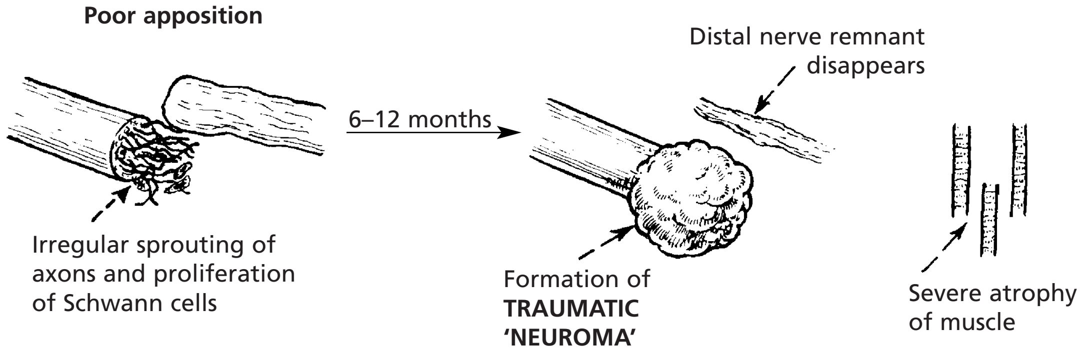
Regeneration takes the form of a sprouting of the cut ends of the axons.



The results depend on the apposition of the distal remnant with the sprouting axons.



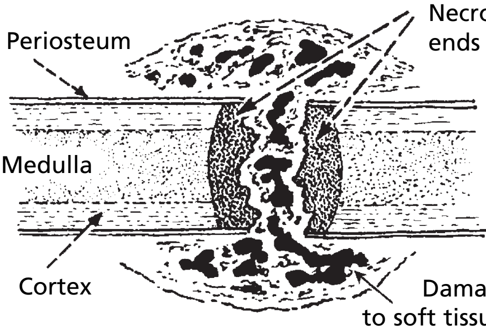
The best results are seen in crushing injuries where the sheaths remain in continuity.



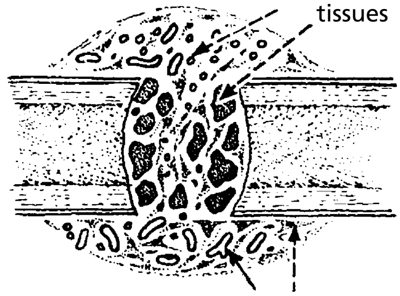
FRACTURE HEALING

BONE – Fracture Healing

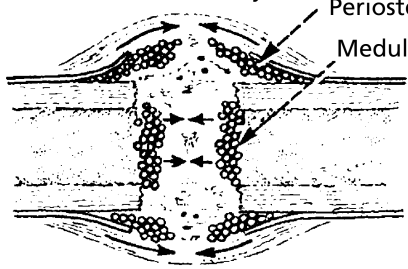
1. *Immediate effects*



2. *Early reaction-inflammatory*
First 4–5 days

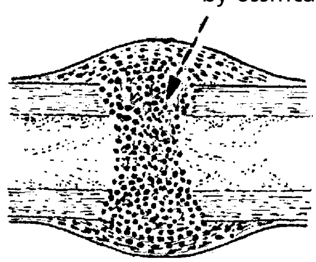


3. *Formation of callus*
(early bone regeneration) – after 1 week.



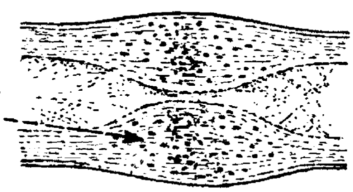
Provisional callus bridges the gap – first, osteoid tissue (may include cartilage) then woven bone

4. *Mature callus*
– from 3 weeks onwards

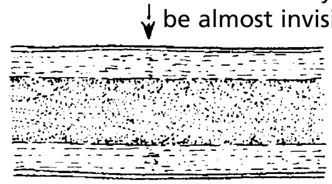


Osteoblastic and osteoclastic activity proceeding

5. *Remodelling of callus*
Definitive – weeks into months



6. *Final reconstruction*
Months later

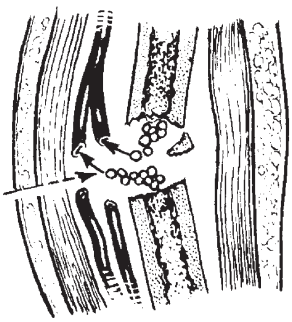


FRACTURE HEALING

Events following a fracture *(continued)*

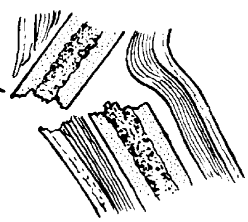
Complications

1. *Fat embolism* may occur in fracture of long bones due to entry of fat from the marrow cavity into the torn ends of veins.

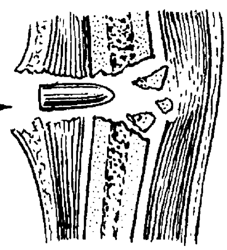


2. *Infection*
   If the overlying skin is breached in any way, i.e. the fracture is 'compound', the risk of infection is greatly increased; this is an important adverse factor in the healing process.

By sharp bone ends



Penetrating injury from outside



PATHOLOGICAL FRACTURE

When the break occurs at the site of pre-existing disease of the bone, the term 'pathological fracture' is applied.

A common condition is a secondary tumour growing in and destroying the bone



Mixture of tumour and haematoma – healing inhibited



Very easily fractured

FRACTURE HEALING

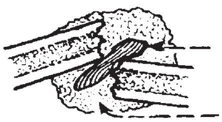
FACTORS INFLUENCING HEALING OF FRACTURES

ADVERSE | **FAVOURABLE**

1. Local factors

(a) *Infection*
(b) *Pathological fracture*
} See previous page

(c) *Poor apposition and alignment* . . . . *Good apposition*



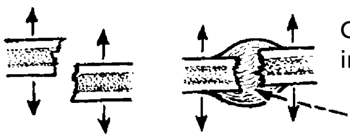
There may be interposition of soft tissue, e.g. muscle

Large irregular callus: slow repair, permanent deformity of bone



Small callus, quick repair

(d) *Continuing movement of bone ends* . . . . *Good immobilisation*



Callus formation inhibited

Fibrous union



Small callus, good bone formation

In extreme cases, a rudimentary joint (pseudoarthrosis) may form



(e) *Poor blood supply* . . . . *Good blood supply*

This is largely influenced by the anatomical site of the fracture, for example:

(a) Nutrient artery entering remote from the fracture or damaged by fracture (e.g. scaphoid, femoral head)
(b) Fracture through area devoid of periosteum (e.g. neck of femur)
(c) Minimal adjacent soft tissue (e.g. tibia).

In favourable conditions blood supply is derived from:

(a) periosteal arteries
(b) nutrient artery
(c) adjacent soft tissues.

2. General factors

(a) *Old age* . . . . *Youth*

(b) *Poor nutrition* – e.g. famine, malabsorption leading to lack of protein, calcium, vit D and vit C. . . . . *Good nutrition* – especially protein, calcium, vit D and vit C.

CHAPTER 4

INFECTION

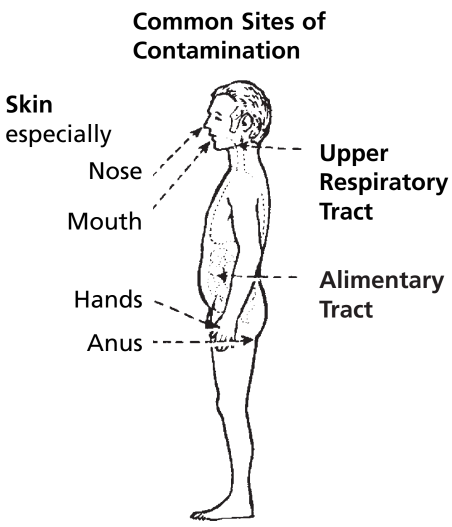
INFECTION

There are very many infections: the chapter will deal only with principles and a few examples.

Type of Infecting Agent	Example	Example of Disease
BACTERIA (a very wide range)	STAPHYLOCOCCUS	ABSCESS
VIRUSES (a wide range)	HERPES ZOSTER	CHICKENPOX and SHINGLES
FUNGI (a limited range)	CANDIDA	BUCCAL and VAGINAL THRUSH
PROTOZOA	PLASMODIUM	MALARIA
Infestation with PARASITES WORMS and FLUKES	ECHINOCOCCUS GRANULOSIS	HYDATID DISEASE

COLONISATION AND COMMENSAL GROWTH

Vast number of bacteria normally colonise the external body surfaces (skin, alimentary and upper respiratory tracts). These **commensal** inhabitants usually do not harm the host. Organisms that injure the host are said to be **pathogenic**. If the host defences are damaged a commensal organism may cause an **opportunistic infection**.



INFECTION AND INFECTIOUS DISEASE

INFECTION occurs when microorganisms invade the sterile internal body tissues. (Multiplication usually follows invasion.)

An INFECTIOUS DISEASE occurs when infection is associated with clinically manifest tissue damage.

Routes of entry of infecting organisms

1. Through the *skin* or *mucous membranes*
   (a) By direct close contact, e.g. venereal disease, HIV.
   (b) By contamination of abrasions and wounds, e.g. wound infections, rabies.
   (c) By inoculation, e.g. insect bite – yellow fever, syringe – hepatitis B and C, AIDS.

2. By *ingestion*
   Contaminated food and water, e.g. enteric fever, hepatitis A, poliomyelitis, cholera.

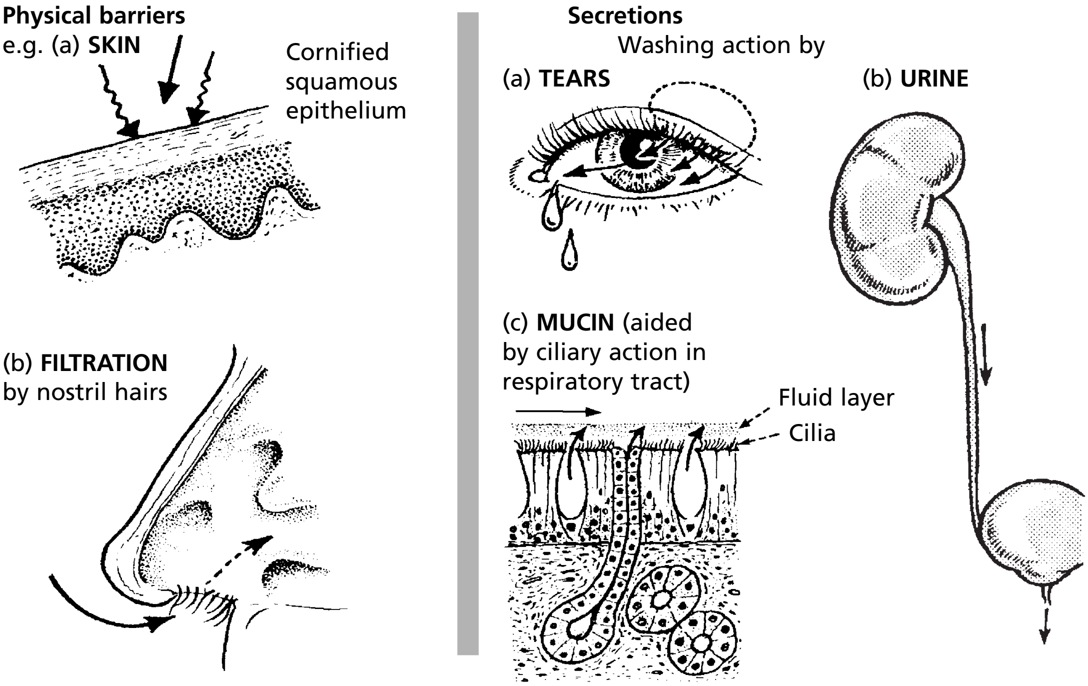
3. By *inhalation*
   Dust and droplets, e.g. influenza: tuberculosis.

INFECTION

Factors influencing the establishment of infection

1. *In the HOST*

In addition to a good state of general health and nutrition, the following mechanisms operate in preventing and limiting infection.



Chemical action
(a) Acid secretion in stomach and urinary tract.
(b) Lysozymes – enzymes capable of dissolving bacterial capsules, e.g. in tears and saliva.
(c) Immunoglobulin A (IgA) – a specialised immunoglobulin (see p.97), – tears, intestinal secretions.
(d) Non-specific inhibitory substances – urine, sweat, sebum.

Innate immune response
(a) NK cells and macrophages.
(b) Plasma proteins including the complement system.

2. *In the MICRO-ORGANISM*

Factors potentiating invasive capacity include:

(a) **Quantity of dose** – the larger the dose the more likely that the defences are penetrated.
(b) **Virulence** – describes the degree of pathogenicity, includes:
  (i) Capacity to resist phagocytosis and enzyme attack,
  (ii) Adhesive properties,
  (iii) Production of exoenzymes which act on host tissues, e.g. hyaluronidase (streptococci), coagulase (staphylococci) and of toxins, e.g. leucocidins, enterotoxins.

INFECTION

Factors influencing the course of infection

Once infection has occurred, important defence mechanisms operate:

1. **Inflammation** in the **acute** local reaction (see p.33) tends to limit the spread of organisms. In some important diseases, there is no acute local inflammatory response at the site of entry, e.g. Brucellosis (undulant fever) and many virus infections. In the **chronic** inflammatory reaction (see p.41), the formation of fibrous tissue also helps to localise infection.
2. **Phagocytosis** (see p.36) *Note:* some organisms may survive or multiply within phagocytes – usually associated with chronic infection. Good examples are tuberculosis, brucellosis, leprosy.
3. **The Immune Response**
   (a) *Humoral antibody* reactions, e.g. agglutination, opsonisation, lysis via complement – especially important in *bacterial* infections.
   (b) *Cellular immunity* reactions, e.g. cytotoxic T cells, especially important in viral infections.
4. **Cytokines** – signalling molecules that regulate the immune response to pathogens.

Examples of failure of protective and defence mechanisms

1. **In skin** – direct breach by wounding and burns; softening of the surface by exposure to water and sweat or due to skin disorders.
2. **In the respiratory tract** – inhibition of ciliary movement by nicotine in smokers potentiates infection.
3. **In the stomach** – in achlorhydria (no hydrochloric acid) organisms flourish in the stomach.
4. **When secretions are prevented from flowing freely** by narrowing of natural passages, bacterial growth in the 'stagnant' fluid is potentiated (e.g. enlarged prostate urethral obstruction, urinary infection).
5. **When commensal growth is impaired** by antibiotic treatment, pathogenic bacteria may colonise the 'vacant site'.
6. **Deficiency of the immunological system:**
   (a) natural deficiency due to hereditary defect, e.g. X-linked agammaglobulinaemia
   (b) acquired due to administration of drugs in treatment of disease, e.g. steroids, cytotoxic drugs; specific virus infection, e.g. Human Immunodeficiency Virus (HIV) causing Acquired Immune Deficiency Syndrome (AIDS).
7. **Deficiency of phagocytosis** – especially polymorphs (either low numbers or deficient function – see page 36).
8. **In debilitating diseases** such as diabetes, chronic failure and nutritional deficiency.
9. **Genetic susceptibility** – may be a factor in some infections.

INFECTION

Mechanisms by which disease is produced

The local reaction to infections is usually INFLAMMATORY and is evoked by cellular damage and death. The detailed mechanisms are different in bacteria and viruses.

BACTERIA

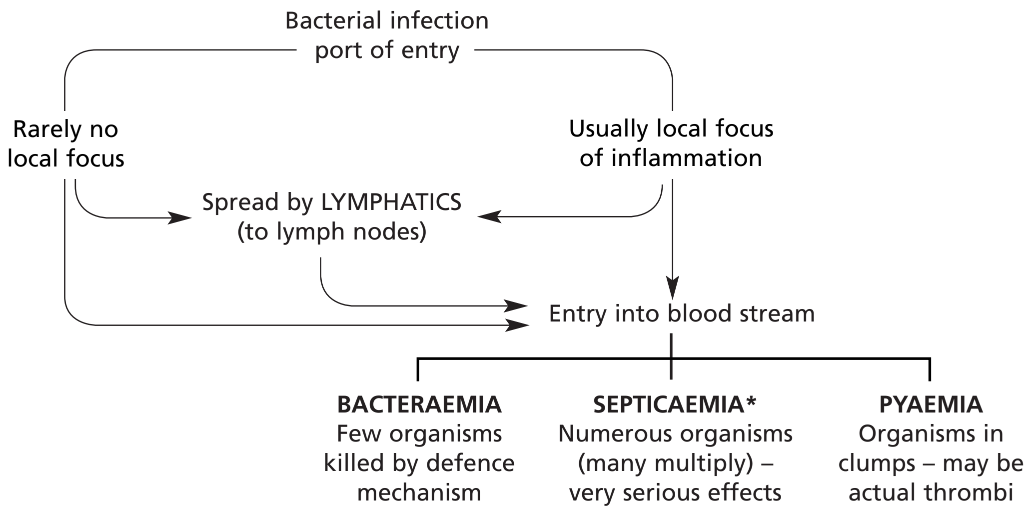
1. **Production of toxins (poisons)**

Exotoxins	**Endotoxins**
Secreted by living bacteria	Integral part of bactrial cell wall Release on death of organism (usually Gram-negative)
Simple proteins	Lipid-polysaccharide complexes
Neutralised by specific antibody (antitoxin)	Do not stimulate antibody production
Many actions – Enzymes, e.g. *S. aureus* protease – Action on intracellular signalling, e.g. *V. cholerae* – Neurotoxins, e.g. *C. botulinum* – Superantigens, e.g. *S. pyogenes*	Beneficialeffects:Inlowdosestimulatesprotectiveimmunity Harmful effects: In high dose ENDOTOXIC SHOCK – due to massive release of cytokines with activation of coagulation,fibrinolytic and complement cascades LPS binds cell surface receptor CD14 and is delivered to TLR4 that starts intracellular signalling cascade

2. **Hypersensitivity reaction causing tissue injury**

This is a form of the immune response in which reaction between the bacterial protein and sensitised lymphocytes initiates the inflammatory reaction (see p.101).

3. **Tissue invasion: lymphatic spread and invasion of blood stream**



*Due to confusion with bacteraemia, many medical professionals avoid septicaemia preferring the term 'sepsis syndrome' (which is the clinical effect of septicaemia).

INFECTION

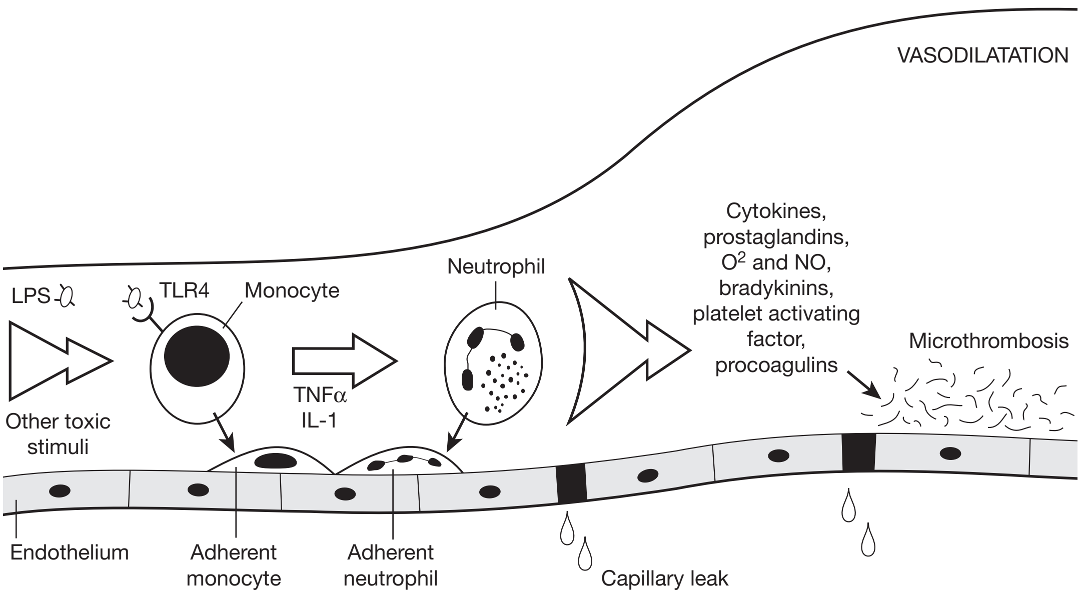
SEPSIS SYNDROME

Sepsis is a very serious condition in which there is a whole-body inflammatory state (systemic inflammatory response syndrome (SIRS)) in the presence of infection.

Mortality is still between 20 and 50% even with modern medical treatment. It commonly occurs in response to lipopolysaccharide (LPS) in the wall of Gram negative bacteria.

Mechanisms

LPS triggers innate immunity via TLR4. With infection disseminated via the bloodstream there is widespread activation of phagocytes.



The initial stimulus triggers production of proinflammatory cytokines, and monocytes and neutrophils adhere to endothelium. Activated macrophages, neutrophils and endothelial cells release secondary inflammatory mediators. This release of proinflammatory cytokines is known as a CYTOKINE STORM. Procoagulants produced by endothelial cells may trigger microthrombosis and if widespread this is known as DISSEMINATED INTRAVASCULAR COAGULATION.

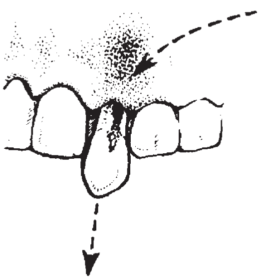
INFECTION

BACTERAEMIA

(a) Occurs commonly: usually of no serious significance
(b) An integral part of some infections, e.g. typhoid fever.

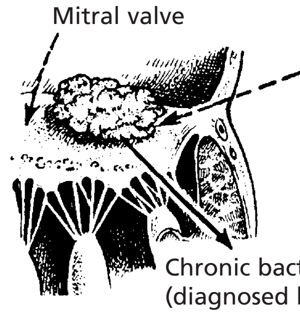
Important special cases

1. *Dental extraction*



Infected tooth
↓ (organisms of low grade virulence)
Bacteraemia
↓
Bacteria may settle on previously diseased heart valves – bacterial endocarditis

2. *Established bacterial endocarditis*

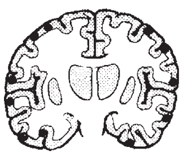


PYAEMIA

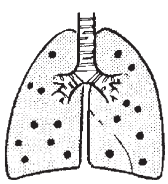
Pyaemia occurs when pathogenic organisms escape into the bloodstream in the form of small aggregates – micro-emboli. This results in either:

PYAEMIC ABSCESSES

Septic focus – usually staphylococcal
↓
Thrombosis of venules incorporating bacteria
↓
Showers of micro-emboli
↓
Multiple micro-absesses in many organs



Cerebral cortex



Lungs

Also heart and kidneys

SEPTIC INFARCTION

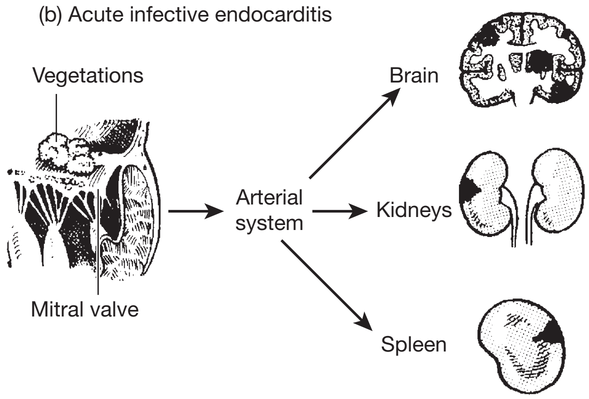
The lesions are larger and less numerous than pyaemic absesses

They are associated with

(a) Septic thrombosis of larger veins (suppurative thrombophlebitis)
e.g. Leg veins → Embolism → Infarction with suppuration in lungs

Portal vein → Embolism → Infarction with suppuration in lungs

(b) Acute infective endocarditis



ACUTE BACTERIAL INFECTION

PYOGENIC BACTERIA

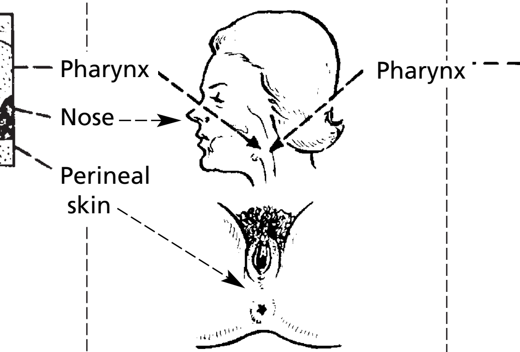
Staphylococcus aureus

Gram-positive spherical organisms in clusters



Produce an enzyme – coagulase – which deposits fibrin at the site and tends to localise the infection with production of an abscess containing pus

Common sites of carriage
(usually without symptoms)



Streptococcus pyogenes

Gram-positive spherical organisms in chains



Produce numerous enzymes, e.g. hyaluronidase – liquifies ground substance; streptokinase – dissolves fibrin: and leucocidin, – kills polymorphs and tends to promote spreading inflammation.

Note: In hospitals staphylococci are becoming increasingly resistant to multiple antibiotics (MRSA = methicillin resistant staphylococcus aureus).

Lesions produced

Skin infections – pustules, oils, carbuncles
Wound infection
Staphylococcal broncho-pneumonia may be a serious complication in epidemic influenza
Exotoxin production → food poisoning: toxic shock syndrome

Skin infections – impetigo, erysipelas, cellulitis
Wound infection
TONSILLITIS and pharyngitis
Exotoxin production
↓
The skin rash of scarlet fever

GENERAL BLOOD SPREAD

PYAEMIA (and septicaemia)
OSTEOMYELITIS – acute inflammation of long bones – particularly in children

SEPSIS SYNDROME

Note: Rheumatic fever and acute glomerulonephritis are complications of streptococcal infection in which the heart and kidneys are damaged. This is caused by disturbance in the immune mechanisms (type III hypersensitivity reaction) and is not due to the actual presence of streptococci in the heart and kidneys.

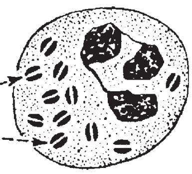
ACUTE BACTERIAL INFECTION

PYOGENIC BACTERIA *(continued)*

NEISSERIA

Meningococcus | **Gonococcus**

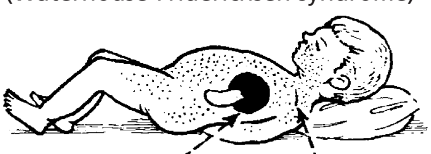
Both are **Gram-negative intracellular** diplococci



Carried in nasopharynx.
Causes **purulent** *meningitis* and, in children, occasionally a fatal septicaemia.

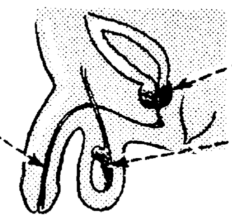
Skin rash — Massive adrenal haemorrhage

(Waterhouse-Friderichsen syndrome)

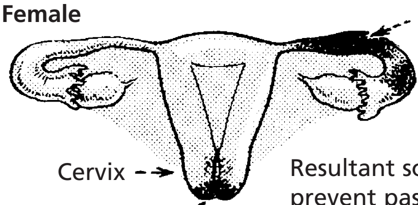


Carried in genital mucous membrane.
Causes purulent inflammation of urethra in male and of uterine cervix in the female with spread to adjacent organs.

Male



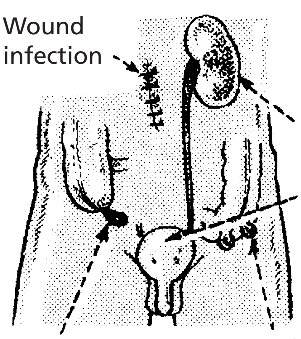
Female



Gram-negative bacilli
These are usually commensals in the alimentary tract and include facultative and obligatory anaerobes.

'Coliform' organisms can cause local inflammation in the alimentary tract, the urinary tract and wound infections.

In addition, ENDOTOXINS liberated in the blood stream cause severe sepsis syndrome with SHOCK (p.174).



FOOD POISONING
E. Coli 0157 – a commensal in cattle is a human pathogen – production of a powerful **virocytotoxin** is associated with the **haemolytic uraemic syndrome** (see p.473) and may cause death in the very young and elderly.

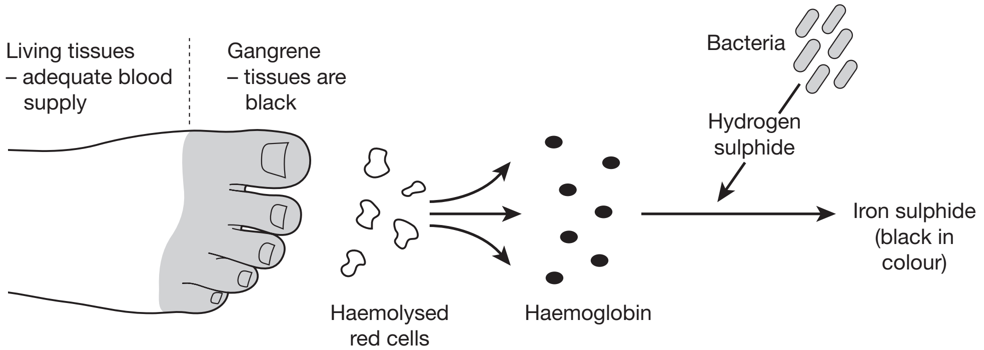
ACUTE BACTERIAL INFECTION

GANGRENE

Gangrene is a complication of NECROSIS in which bacterial infection is superimposed. There are three main types:

1. Dry gangrene

This occurs in the toes and feet of elderly people or diabetics suffering from gradual arterial occlusion. The putrefactive process spreads slowly until it reaches the part where the blood supply is adequate. Small numbers of organisms are present.



2. Wet gangrene

The tissues are moist at the start of the process due to venous congestion or oedema, e.g. strangulation of viscera. The disease spreads rapidly and may be associated with sepsis syndrome. Tissue discolouration occurs by the same mechanism as dry gangrene.

3. Gas gangrene

Dry and wet gangrene are associated with mixed bacterial infection. Gas gangrene is caused by exotoxin producing bacteria of the CLOSTRIDIA group – ANAEROBIC sporulating Gram-positive bacilli (*Cl. perfringens* most common). These organisms, found in soil, can enter a wound and proliferate in necrotic tissue with formation of gas bubbles. Spread is rapid with sepsis syndrome. It is a serious complication of war wounds.

Special types of gangrene

Necrotizing fasciitis – this infection spreads along fascial planes within subcutaneous tissue. The infection may be polymicrobial or due to a single organism, commonly group A streptococcus or, in hospitals, MRSA.

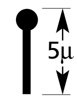
Fournier's gangrene – this is a form of necrotizing fasciitis affecting the male genitals particularly in diabetics.

ACUTE BACTERIAL INFECTION

TETANUS

This organism itself does not cause local tissue damage. The effects are due to a powerful ENDOTOXIN secreted by the organism. This is in contrast to the usual bacterial diseases where tissue damage is important and is due to the local bacterial action.

The infecting organism, *Clostridium tetani*, a STRICT ANAEROBE, is a Gram-positive rod. Often the presence of a terminal spore gives a characteristic drum-stick appearance. The highly resistant spores are widespread in the environment due to contamination by animal faeces.



Method of Infection

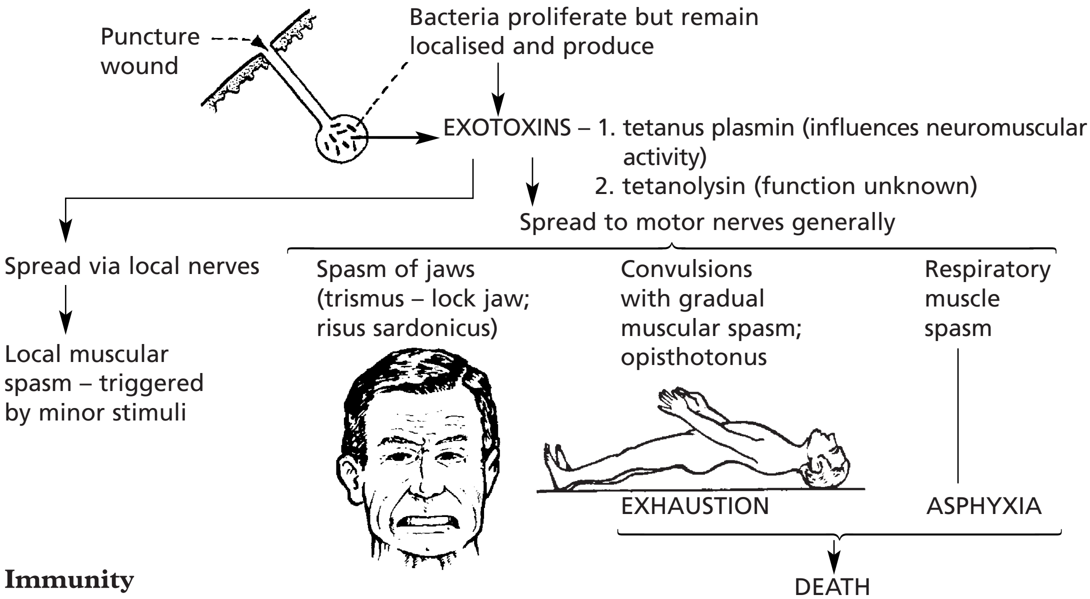
Contamination of wounds in which there are anaerobic conditions, e.g. deep-penetrating wounds and wounds with severe soft tissue damage (road traffic accidents and battle casualties); only very occasionally trivial thorn punctures.

In developing communities the umbilical stump of the newborn may be infected by faecal material.

Effects

The exotoxin is highly potent and causes paroxysmal muscular spasm which becomes progressively more severe and was fatal in many cases: modern therapy including muscle relaxation and ventilation has improved the prognosis dramatically.

Course



Immunity

- Active immunisation by **TOXOID** — prophylactic.
- Passive immunisation by **ANTITOXIN** — therapeutic (only effective before toxin is fixed to nerve tissues).

Other important bacteria producing toxins are: *Clostridium botulinum* (botulism), *Vibrio cholerae* (cholera), *Corynebacterium diphtheriae* (diphtheria).

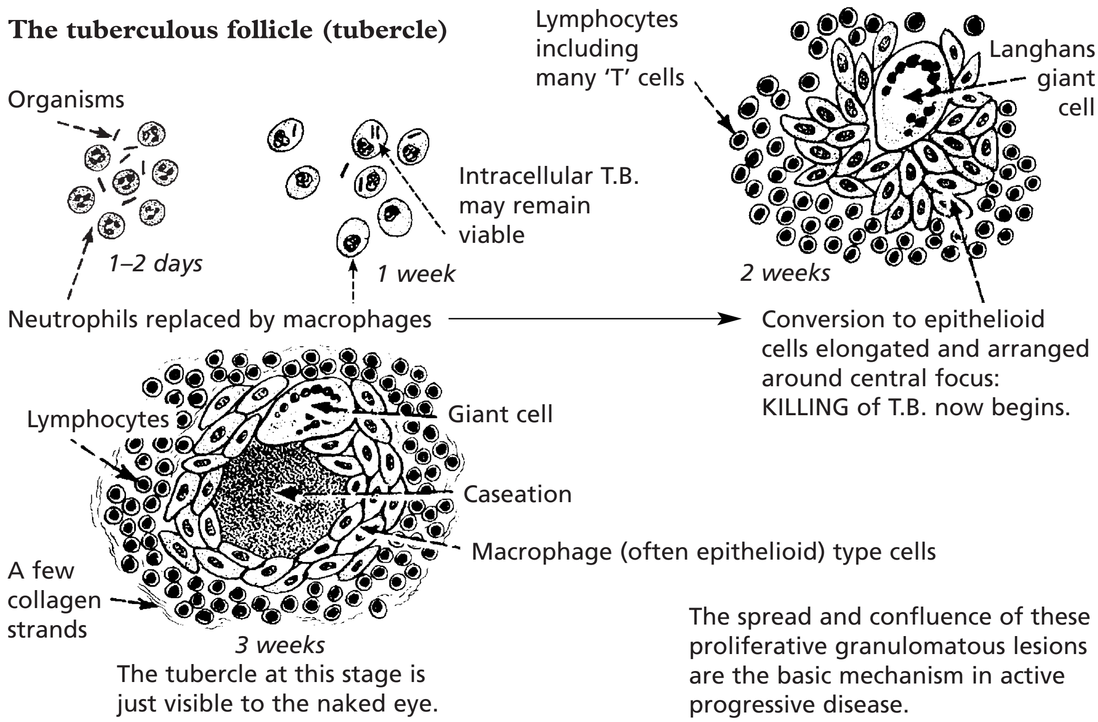
CHRONIC BACTERIAL INFECTION (GRANULOMAS)

In these infections chronic inflammation is the basic mechanism (see p.42). The detailed evolution of the inflammatory reaction is modified by several factors of which the immune response of the host is important (see p.89).

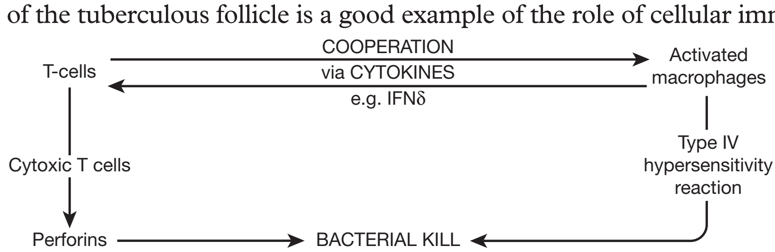
TUBERCULOSIS

Tuberculosis is caused by the *Mycobacterium tuberculosis* (tubercle bacillus: TB), an organism which has a resistant waxy component in its structure and is acid and alcohol-fast (i.e. resists bleaching with strong acid and alcohol after being stained red with fuchsin). The disease rapidly declined in Western Europe and North America after World War II due to (a) improved nutrition and hygiene, (b) BCG immunisation and (c) chemotherapy (*note:* drug resistance is becoming an increasing problem). Patients with AIDS are at particular risk: other 'at risk' groups are the elderly, the immunosuppressed and alcoholics. The disease remains prevalent in developing countries.

The tuberculous follicle (tubercle)



The evolution of the tuberculous follicle is a good example of the role of cellular immunity (p. 92)



The caseation is the result of the combined effects of (a) the type IV hypersensitivity reaction, (b) bacterial activity and (c) ischaemia.

CHRONIC BACTERIAL INFECTION (GRANULOMAS)

OTHER MYCOBACTERIAL INFECTIONS

Mycobacteria other than tubercle sometimes infect humans. They are commonly present in soil and water and are less virulent than *M. tuberculosis*. Most exposures do not produce disease unless there is a defect in local or systemic host defenses.

M. avium and *M. intracellulare* – these are closely related and are often grouped together as *M. avium-intracellulare* (MAI) – they may cause pneumonia, lymphadenitis or disseminated disease in immunosuppressed patients.

M. kansasii – this may cause a chronic cervical lymphadenitis with cutaneous fistulas and scarring in children.

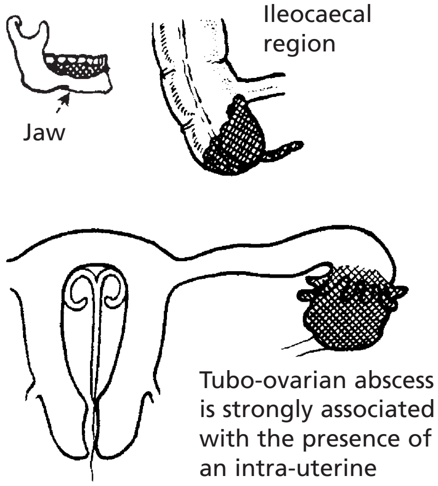
M. marinum – this can cause a cutaneous granulomatous ulcerating lesion which can be contracted from contaminated swimming pools or from cleaning an aquarium (swimming pool granuloma).

ACTINOMYCOSIS

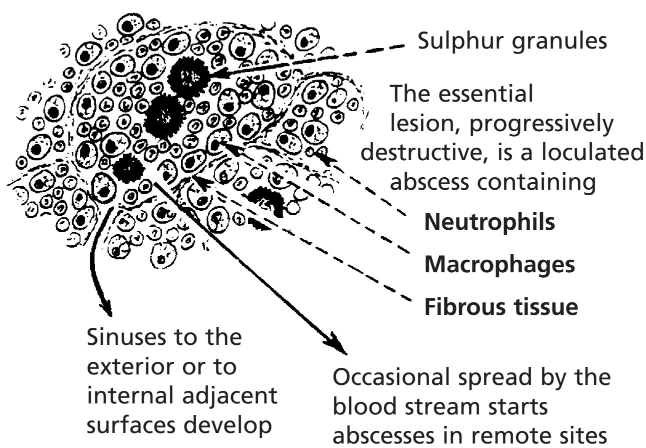
Actinomycosis is a localised but gradually spreading chronic suppuration affecting the lower jaw, the ileocaecal region of the bowel, the female genital tract and occasionally the lung.

The organism – *Actinomyces israelii* – widespread in nature, is a Gram-positive, branching, filamentous anaerobe found around the teeth and in the pharyngeal crypts. In the tissues, it forms yellow, densely felted together spherical colonies just visible to the naked eye: the pus is seen to contain ‘sulphur granules’.

Sites of infection



Abscess formation



CHRONIC BACTERIAL INFECTION (GRANULOMAS)

LEPROSY

This slowly progressive disease which causes serious effects by damage to peripheral nerves is still widespread in the tropics and subtropics. The infection is acquired by close, prolonged contact and is due to *Mycobacterium leprae*, a slender acid and alcohol-fast bacillus. The disease presents in two contrasting extreme forms and with cases of intermediate type.

1. Lepromatous leprosy	2. Tuberculoid leprosy
Disfiguring nodularity of the skin – 'leonine facies'.	Focal areas of skin pallor and anaesthesia due to early involvement of nerves.
Peripheral nerves affected late.	Basic lesion is a follicular granuloma (tubercle) not unlike the true tubercle follicle.
The lesions contain lymphocytes, plasma cells and macrophages – filled with organisms.	
Organisms + + + in tissues.	Organisms are scanty.

These differences are due in the main to differences in the immune reaction of the host.

A defective Th1 response or dominant Th2 response.	A predominant Th1 response with IL2 and IFNγ production.

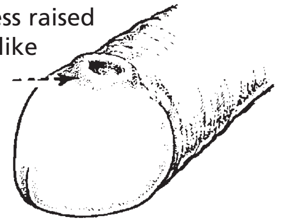
SYPHILIS

This is a sexually transmitted disease caused by a spirochaete (*Treponema pallidum*). It has a close set spiral structure that can be demonstrated by dark ground illumination, silver staining of immunofluoresence. The incidence of syphilis declined until the late 1990s but there has been a marked increase in cases since 2001 particularly in homosexual males.

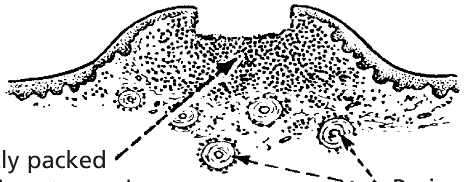
PRIMARY SYPHILIS

During the first three weeks after infection, the spirochaetes spread in the blood throughout the body without any noticeable effects. Then the primary lesion – hard chancre – appears at the original site of entry.

The INGUINAL LYMPH NODES present clinically as painless, firm swellings due to proliferation of lymphocytes and plasma cells.



Diagnosis is by examination under dark ground illumination of serum taken from ulcer.



Note: No neutrophils: this is not an abscess. There is minimal tissue destruction and healing occurs without scarring.

CHRONIC BACTERIAL INFECTION (GRANULOMAS)

SECONDARY SYPHILIS

During the next 2 or 3 months, the spread of the organisms throughout the body causes secondary stage effects. These are a widespread rash (pox) of varying appearance, ulceration of mucous membranes, generalised lymphadenopathy, damage to various individual organs and tissues. There are constitutional effects – particularly fever and anaemia.

The essential pathology is the presence of very numerous spirochaetes accompanied by focal infiltration of lymphocytes, plasma cells and macrophages with mild arteritis. Infectivity is very high. Tissue destruction is minimal and healing occurs without scarring. A latent stage of long duration is followed in 35% of cases by tertiary syphilis.

TERTIARY (LATE) SYPHILIS

The lesions, which may occur at any time for many years after the healing of the secondary phase, offer striking contrasts. This stage is characterised mainly by local destructive lesions, the result of cellular immunity (T cells) causing necrosis of tissue. The main forms are:

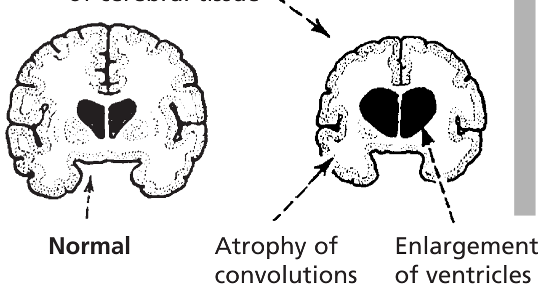
1. **Gumma**, 2. **Syphilitic aortitis** and 3. **Neurological syphilis**.

1. **Gumma**
   This is a localised area of necrosis which may affect large parts of any organ or tissue but particularly bones, testis and liver.

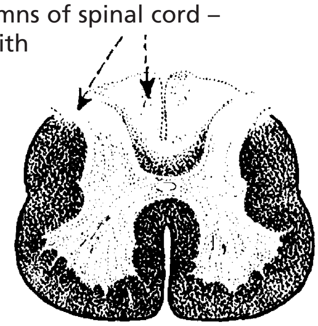
2. **Syphilitic aortitis**
   The arch and thoracic aorta is damaged with weakening of the media: this leads to ANEURYSM formation (see p.231) which causes serious local pressure effects and may also rupture with severe haemorrhage.

3. **Neurological syphilis**
   (a) **Meningovascular** – mainly affects the meningeal blood vessels and causes neurological impairment secondarily.
   (b) **Parenchymatous**

(i) General paralysis of the insane – severe destruction of cerebral tissue



(ii) Tabes dorsalis – the damage specifically affecting the posterior roots and columns of spinal cord – is associated with characteristic clinical symptoms due to loss of proprioceptive sensation in the legs



CHRONIC BACTERIAL INFECTION (GRANULOMAS)

CONGENITAL SYPHILIS

Transplacental infection of the fetus occurs with the following possible consequences:

(a) abortion or stillbirth – many organs damaged

(b) birth of marasmic infant – organ and tissue damage at birth and in later childhood.

DIAGNOSIS OF SYPHILIS

1. **Demonstration of organisms**

   In primary syphilis and early secondary syphilis organisms may be detected in smears from lesions by dark-ground microscopy.

2. **Serological tests**

   (a) *Screening tests*

   The Venereal Diseases Reference Laboratory (VDRL) and rapid plasma reagin (RPR) test both detect non-specific antibodies in the blood of patients that may indicate that the patient has syphilis. They do not detect antibodies to the bacterium but rather against substances released by cells when they are damaged by *T. pallidum*. False positives can occur.

   (b) *Specific tests*

   Specific anti-treponemal antibodies are detected in the *T. pallidum* haemagglutination assay (TPHA) and fluorescent treponemal antibody-absorption (FTA-ABS) assay.

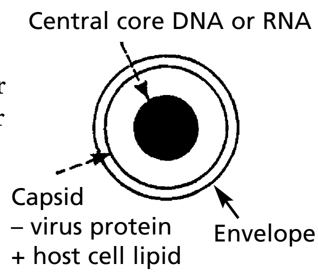
OTHER SPIROCHAETE INFECTIONS

Borrelia burgdorferi is transmitted to humans by deer tick bites and causes Lyme disease – symptoms include a rash, arthralgia and occasionally meningitis.

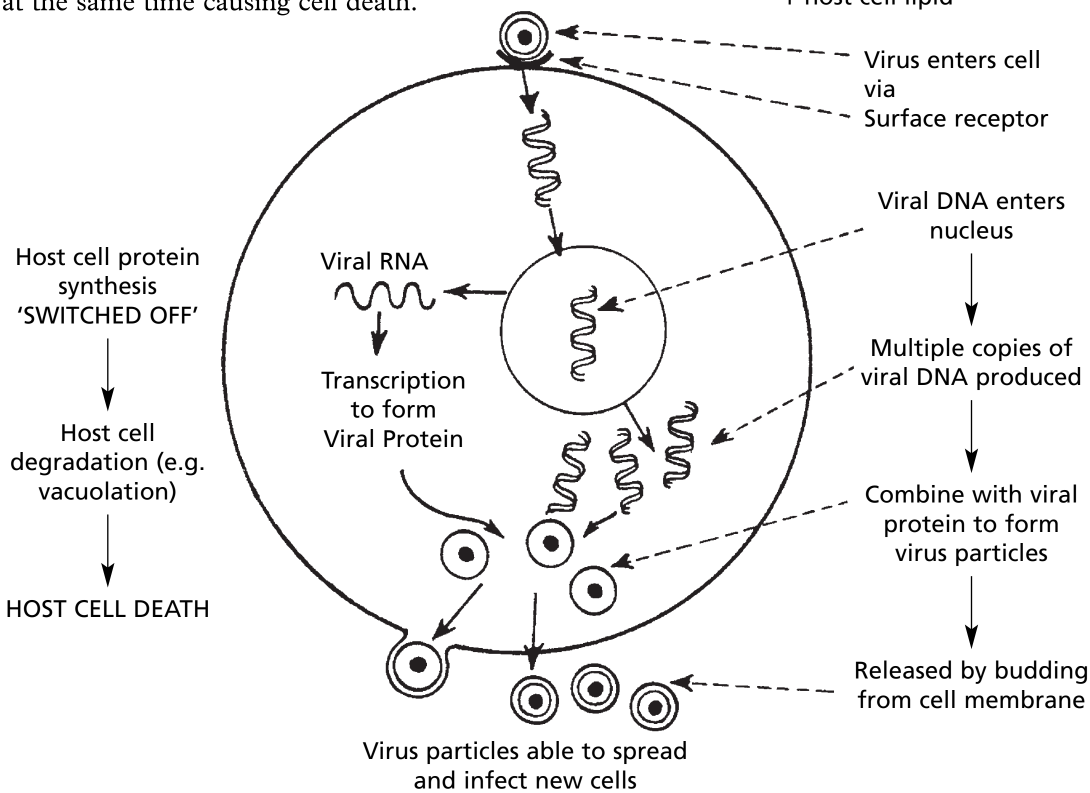
VIRUS INFECTIONS

VIRUS INFECTIONS

Viruses are obligate intracellular pathogens that can replicate only by utilising the resources of the infected cell. The virus particle, or *virion*, consists of a central core of genetic material, either RNA or DNA, surrounded by a protein coat (*capsid*). In addition there may be a membranous *envelope* containing host and viral lipids.



The diagram shows DNA virus using the host cell for replication: at the same time causing cell death.



In addition to this direct cytopathic effect of the virus, damage to host may also be caused by:

(i) Side effects of the immune response.
(ii) Incorporation of virus into the cell genome severely affecting the intracellular metabolism.

RETROVIRUSES

An important variation occurs in a small group of RNA viruses. These contain an enzyme – **reverse transcriptase** – which, within the cell cytoplasm, is able (using the virus RNA as the template) to synthesise virus DNA which is then incorporated into the nuclear genetic material (note that messenger RNA is not required).

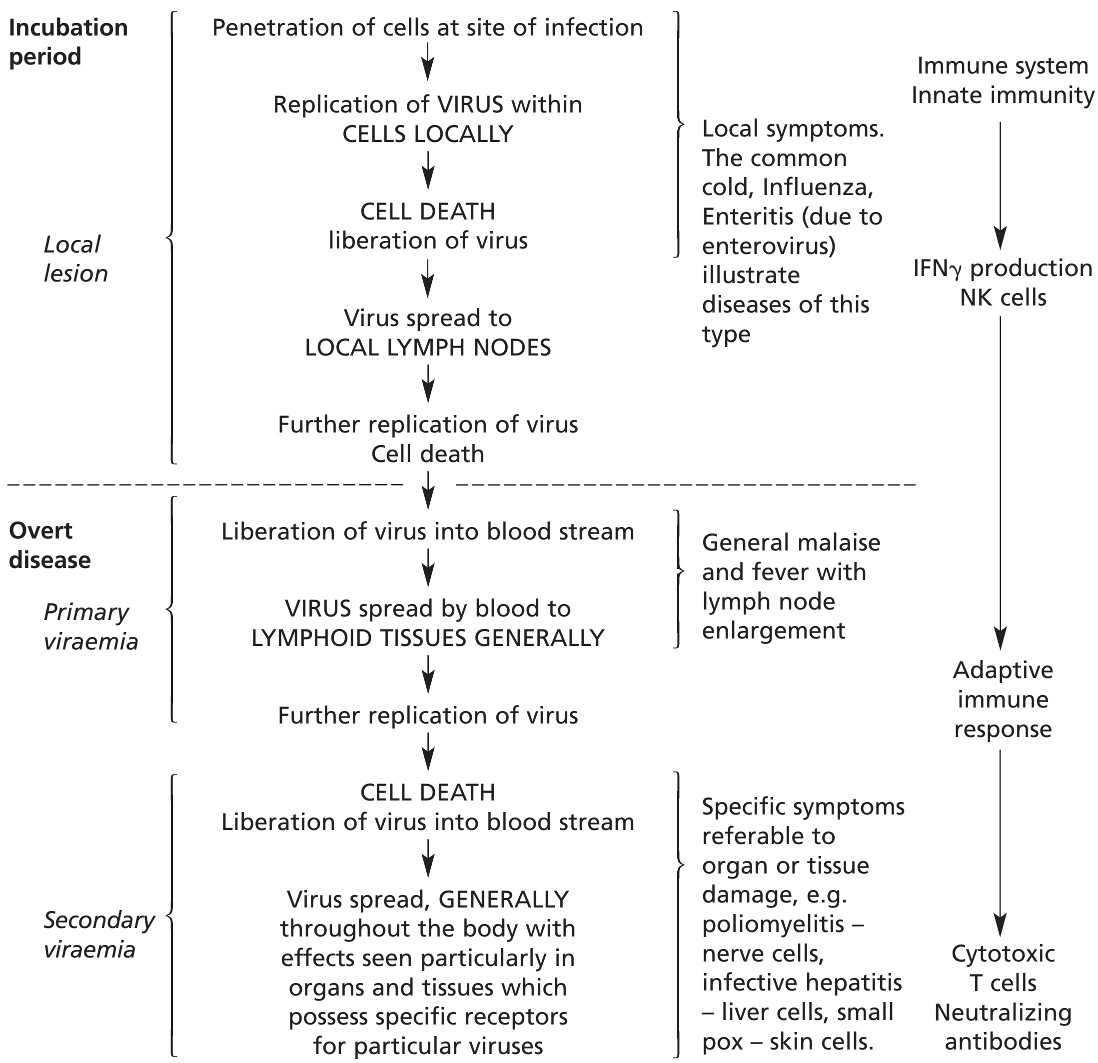
The virus DNA may remain there inactive for long periods. When activity is resumed, replication and cytopathic changes are effected as indicated in the diagram. Retroviruses are important agents in carcinogenesis and AIDS (see p.105).

VIRUS INFECTIONS

ACUTE VIRUS INFECTION

The evolution of a typical acute virus infection can be understood in terms of virus replication, release and spread within the body, and of the host's reaction.

Typical evolution



This typical evolution is produced by successive waves of virus. However, the great majority of virus infections are clinically latent or mild because virus replication and spread are prevented by the body's defence mechanisms. Severe overt disease occurs when there is a specially virulent virus or when the body's resistance is inadequate, especially in a primary infection.

Not all virus infections cause disease in this way, 2 important variations are:

1. LATENT and 2. ONCOGENIC

VIRUS INFECTIONS

LATENT VIRUS INFECTION

A good example is the common 'cold sores' of the lips and face caused by the virus Herpes simplex (an enveloped DNA virus).

Initial infection



Mother (with herpes) kissing infant may → result in trivial or unnoticed blister → VIRUS moves to sensory nerves and lies LATENT → NOT INFECTIOUS TO OTHERS

Reactivation

At any time non-specific 'triggering' may occur, e.g. associated with 'cold', 'flu', sunbathing

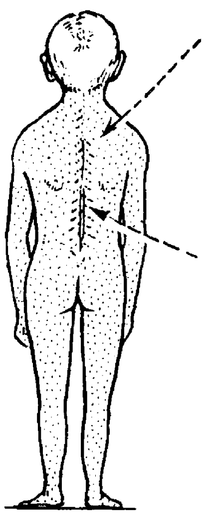


Virus replicates in nerves and travels to site of primary infection, often mucocutaneous junction. Recurrent cold sores INFECTIOUS TO OTHERS

Another example is **herpes zoster (shingles).**

This is a painful affection of segmental sensory nerves and root ganglia due to infection by CHICKEN POX VIRUS **Varicella**.

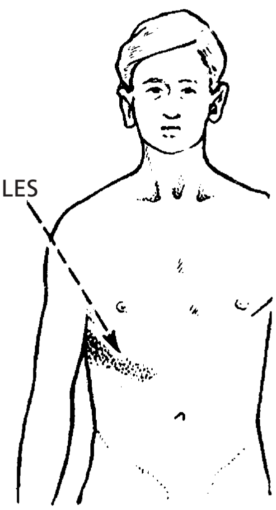
Initial infection in childhood



Generalised vesicular skin rash → INFECTIOUS

RECOVERY but VIRUS DNA lies LATENT in DORSAL ROOT GANGLIA → NOT INFECTIOUS

MANY YEARS LATER REACTIVATION OCCURS → SHINGLES



Virus moves down sensory nerve to skin. PAIN and vesicular rash usually confined to the distribution of a single sensory nerve e.g. intercostal → INFECTIOUS

If the trigeminal nerve is affected serious damage to the eye may result.

VIRUS INFECTIONS

ONCOGENIC VIRUS INFECTION

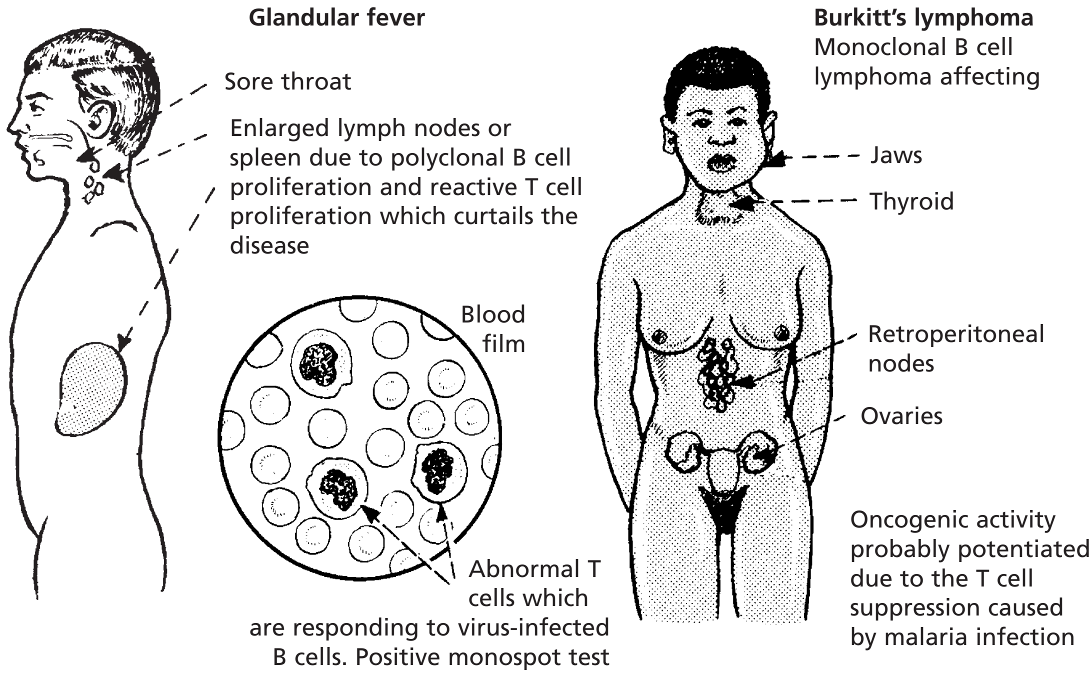
Several DNA viruses and retroviruses of the RNA family can give rise to tumours (see also p.150).

Examples include the following:

(a) Human Papilloma Virus (HPV) – HPV-16 and 18, strains of the common wart virus, are the primary cause of cervical carcinoma. Young girls are now vaccinated against HPV to reduce the incidence of cervical cancer.

(b) Hepatitis Virus – both hepatatis B and C viruses are firmly associated with hepatocellular carcinoma whether sufferers develop cirrhosis or not.

(c) Epstein-Barr Virus (EBV) – a member of the herpes group causes glandular fever (infectious mononucleosis – a non-malignant condition) in young adult in Western societies. This virus is also closely associated with Burkitt's lymphoma (a malignant tumour) found in young Africans living in malarial areas, nasopharyngeal carcinoma particularly in the Far East, with Hodgkin's disease and with post transplant lymphoma.



(d) Retroviruses – T-cell leukaemias are caused by specific retroviruses, i.e. human T cell Leukaemia-Lymphoma Virus (HTLV). HTLV-1 is endemic in Japan, the West Indies and central belts of Africa.

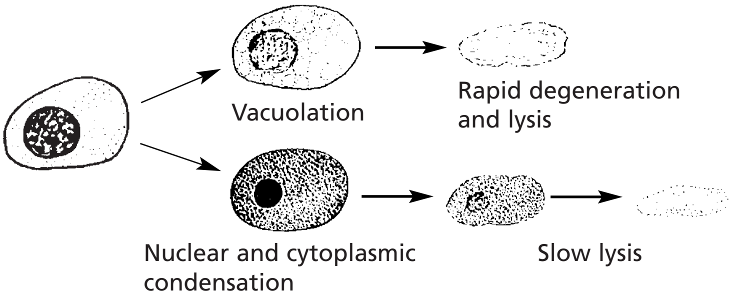
The mechanisms by which viruses cause tumours are illustrated on page 150.

HOST/VIRUS INTERACTION

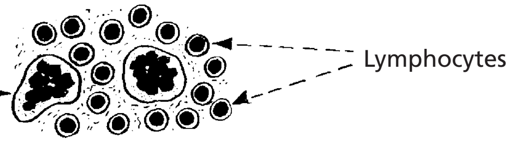
The reactions occurring in the host are important.

1. **Changes in the infected cells**

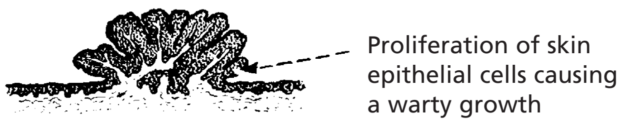
(a) Cell degeneration (with loss of function) leading to cell death.



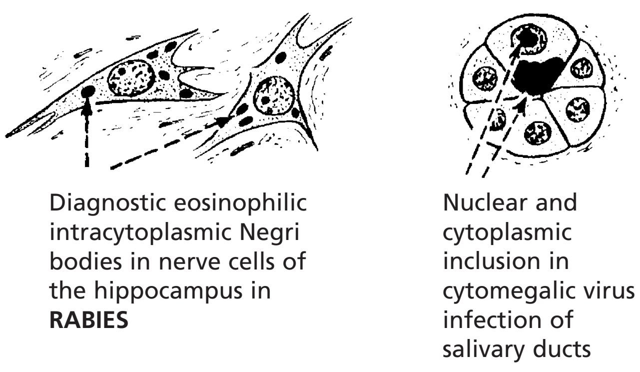
(b) Fusion of adjacent infected cells – giant cell formation, e.g. the Warthin-Finkeldy cell of measles



(c) Cell proliferation, e.g. common wart of HPV infection.



(d) Formation of 'inclusion' bodies within cytoplasm or nucleus: they consist of aggregates of virus and/or products of cell degeneration.



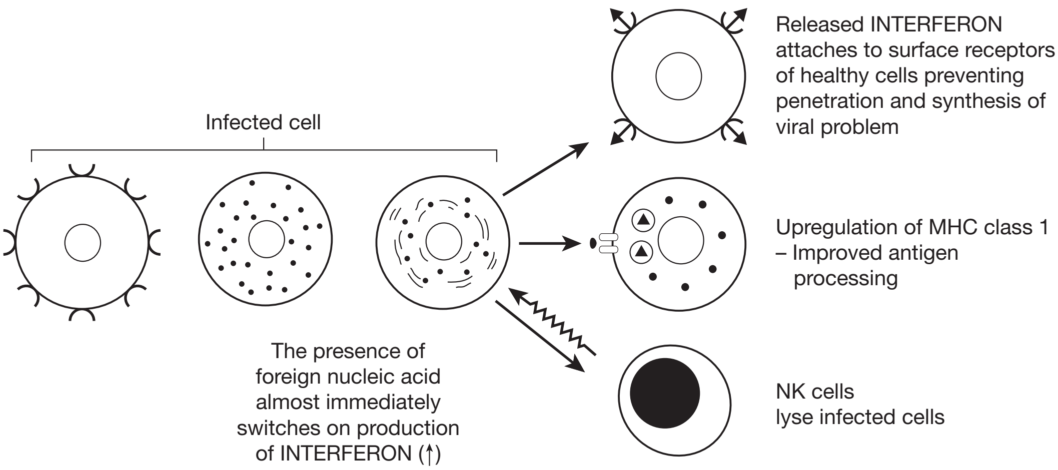
(e) No apparent change in cell but virus remains latent – reactivation later with continuous and slow release associated with gradually progressive disease.

(f) No apparent change but later malignant proliferation occurs, i.e. oncogenic infection.

HOST/VIRUS INTERACTION

Reactions in host *(continued)*

2. **Interferon production** by the infected cells and specifically activated T lymphocytes. Interferons are a group of protein molecules – not antibodies. They represent the first and very important line of defence by interfering with the synthesis of viral protein and thus protect healthy cells. Interferons also stimulate production of MHC class I molecules and special proteins that enhance the ability of virally infected cells to present viral peptides to T cells. They also activate NK cells.



3. **The adaptive immune response** (see p.89) begins 4–7 days after initial infection.
   (a) Antibodies to virus } limit initial infection via antibody-dependent cell-
   (b) Cellular immunity } mediated cytotoxicity (ADCC) but are very important in protecting against RE-INFECTION.
   (c) Occasionally virus antibody complexes cause special types of reaction in the host, e.g. inflammatory necrosis of arteries (arteritis), some forms of kidney damage, and the skin rashes of childhood viral infections.

4. **The inflammatory response**
   The vascular and exudative elements follow the usual pattern; **neutrophils** are **not** a feature unless there is considerable tissue necrosis or secondary bacterial infection. However, **macrophage** phagocytic activity is important in the defence against viral infection. There is often a relative **lymphocytosis**.

OPPORTUNISTIC INFECTIONS

This term is used for infections caused by organisms which are often nonpathogenic or of low grade virulence, occurring in individuals whose resistance to infection is impaired. They are occurring more frequently in modern medical practice because of the increasing use of powerful immunosuppressive drugs.

CAUSES OF LOWERED RESISTANCE

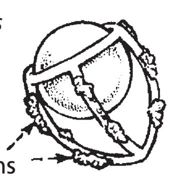
1. Congenital immunological deficiencies (rare).
2. Acquired
   (a) *the result of disease:* HIV infection (AIDS); uraemia; liver disease; malignant tumours, particularly Hodgkin's disease and leukaemias;
   (b) *the result of therapy:* e.g. immunosuppression in transplant surgery; immunosuppression – a side effect of tumour therapy; antibiotics – changing commensal populations;
   (c) *introduction of foreign material:* e.g. heart valve prostheses; I.V. long lines in intensive care; tracheostomy.

Examples of infecting organisms

Bacteria → *Acinetobacter* wound infections: septicaemia

↓

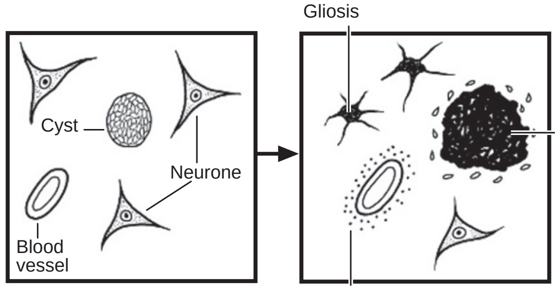
Staph. epidermidis on heart valves; low grade septicaemia



Vegetations on artificial heart valve

Protozoa

Toxoplasma gondii reactivation of latent infection causes encephalitis (particularly in AIDS patients)

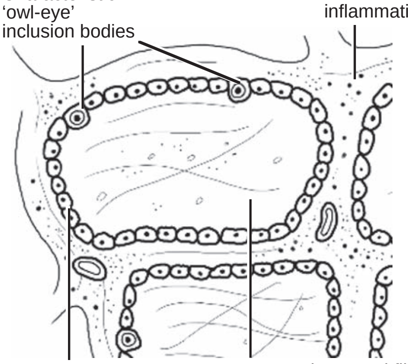


Dormant cyst in brain of immuno-competent person

Reactivation of this cyst in immuno-suppressed patient leads to encephalitis

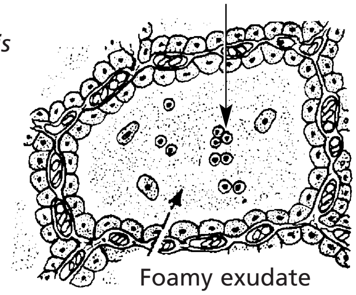
Virus

Cytomegalovirus pneumonia



Fungi

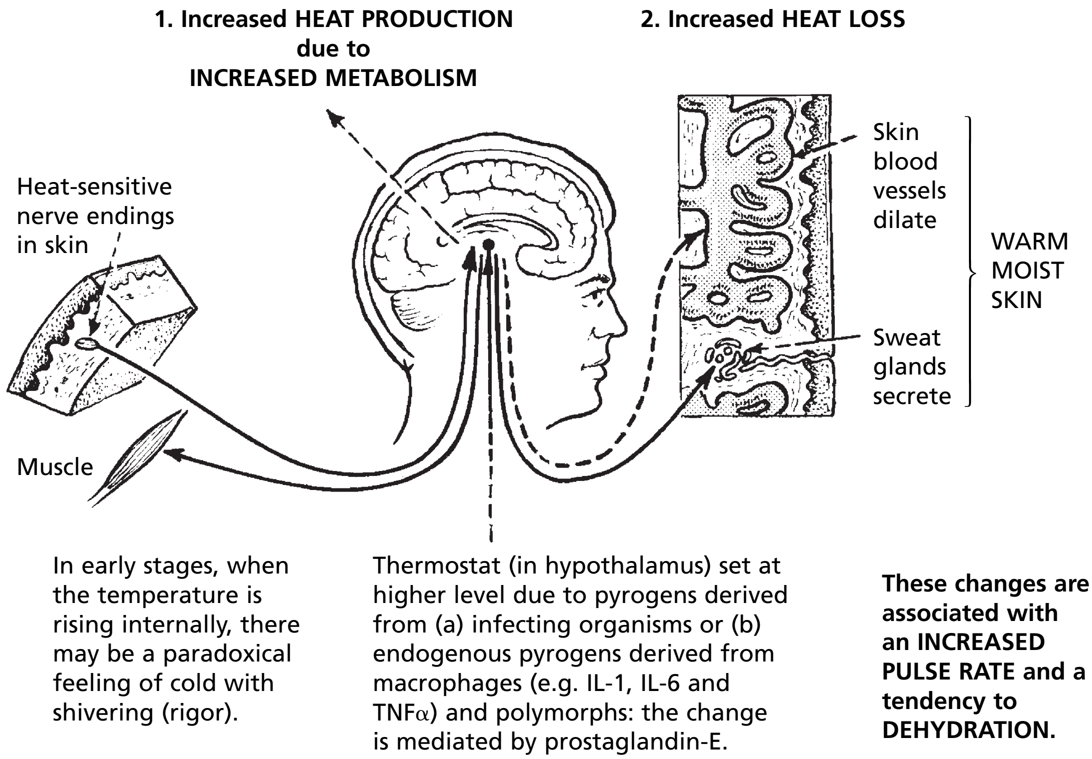
Pneumocystis jiroveci (previously known as *carinii*) a severe pneumonia (seen in AIDS cases particularly)



INFECTION – GENERAL EFFECTS

The more general body reactions in infection are: FEVER and CHANGES IN METABOLISM.

FEVER (PYREXIA)
The body temperature rises above normal initially due partly to an imbalance between heat production and loss, but mainly due to a resetting at a higher level of the 'thermostat' mechanism in the hypothalamus. This results in:



Pyrexia also occurs when there is:

(a) Considerable tissue necrosis, e.g. infarction and tumours

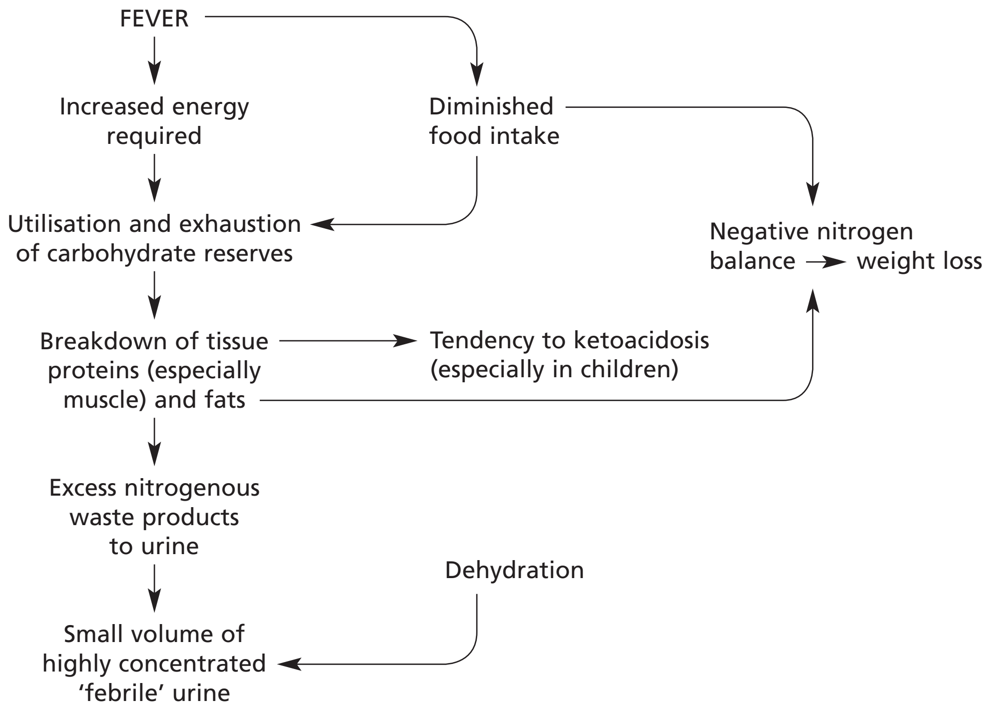
(b) Cerebral disease – especially in the region of the pons.

(c) Heat-stroke – where the environmental temperature and humidity are high and there is excessive water and salt loss.

Hyperpyrexia (when the temperature exceeds 41°C (106°F)) is extremely dangerous because of damage to the nerve cells in the brain.

INFECTION – GENERAL EFFECTS

CHANGES in METABOLISM
Tissue breakdown is greatly increased, and in some infectious fevers there is a marked loss of body weight.



CHANGES in the BLOOD

(a) (i) **Neutrophil leukocytosis** – in acute bacterial infections.

(ii) **Lymphocytosis** – often in viral infections.

(iii) **Lymphopenia** – in typhoid fever and chronic debilitating infections.

(b) **Biochemical changes**

(i) **Non-specific** changes in plasma proteins → cause a rise in the **Erythrocyte Sedimentation Rate (ESR).**

(ii) Specific antibodies are present in both bacterial and viral infections (See next chapter).

(iii) Acute Phase Proteins – a group of serum proteins which rise in response to inflammation: examples are C-reactive protein (used in diagnosis): complement components: mannin-binding lectin (MBL) and serum amyloid A protein: in long-standing chronic inflammation AMYLOIDOSIS may be a complication (see p.24).

(iv) Other chemical changes are listed on page 36.

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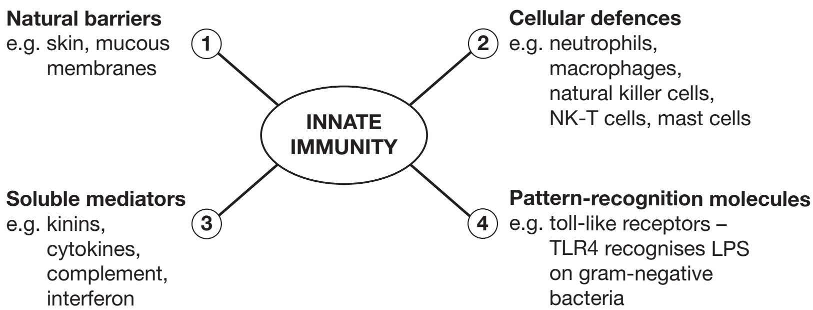
CHAPTER 5

IMMUNITY

IMMUNITY

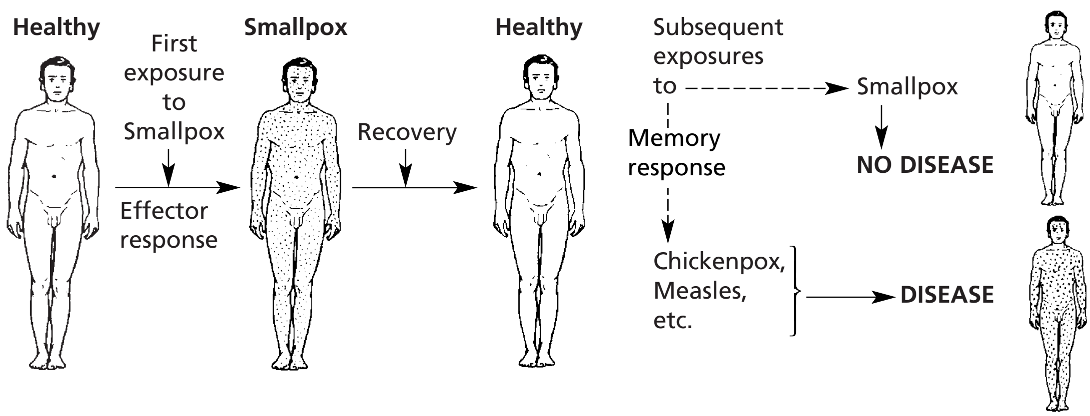
The immune system protects us from invading pathogenic microorganisms and cancer. Immunity – the state of protection from infectious disease – has both a less specific or INNATE and a more specific or ADAPTIVE component.

INNATE IMMUNITY
This provides the first line of defence against infection. It is a rapid response (minutes); it is not specific to a particular pathogen. It has no memory and does not confer long-lasting immunity to the host. It has 4 main components and is found in all classes of plant and animal life.



ADAPTIVE IMMUNITY
This provides a specific immune response directed at an invading pathogen. Following exposure to a foreign organism there is an initial EFFECTOR RESPONSE that eliminates or neutralizes a pathogen. Later re-exposure to the same foreign organism induces a MEMORY RESPONSE with a more rapid immune reaction that eliminates the pathogen and prevents disease. This response is found only in vertebrates.

It has been known from historical times that a person who has recovered from an infectious disease, e.g. smallpox, is most unlikely to suffer from it again – even when exposed maximally – although he would remain susceptible to other infections.

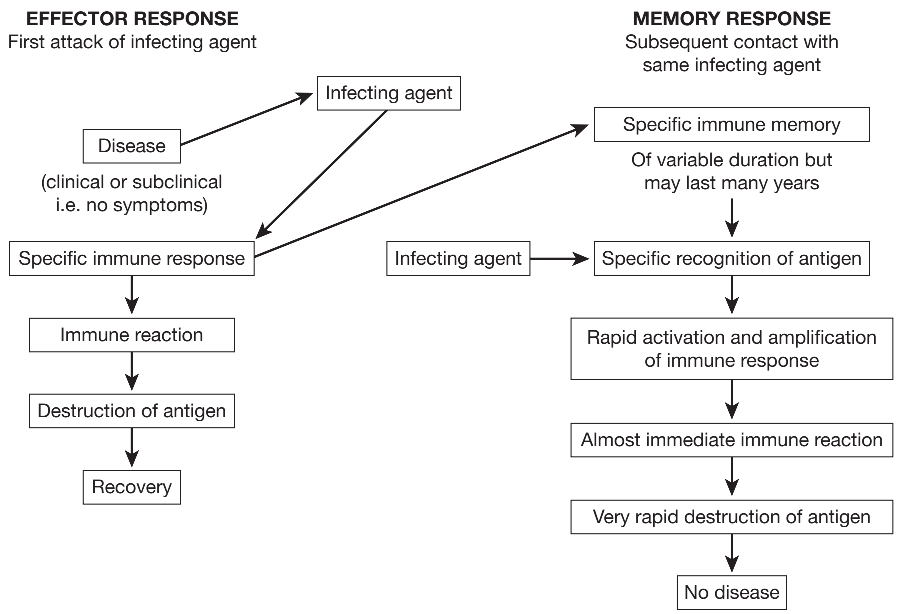


That is, during the recovery period he has ACQUIRED SPECIFIC IMMUNITY to smallpox but not to other unrelated infections.

Note: This immunity may extend to related infections: the use of the immunity against smallpox conferred by world-wide vaccination with cowpox (pioneered by Jenner in the 18th century) has completely eliminated smallpox throughout the world.

THE ADAPTIVE IMMUNE RESPONSE

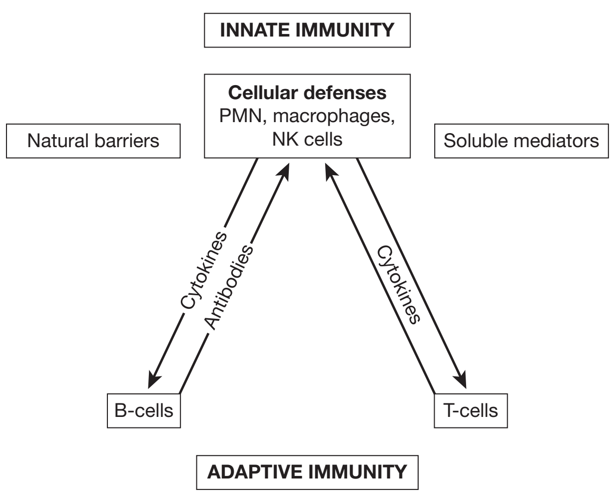
ADAPTIVE IMMUNE RESPONSE



ANTIGENS – Substances that can be recognised by the immunoglobulin receptor of B cells or the T cell receptor when complexed with MHC are called ANTIGENS. They are usually part of infectious agents such as bacteria and some viruses although other foreign materials are also antigenic. Most antigens are proteins but some large carbohydrate molecules such as lipopolysaccharides will induce antibody formation.

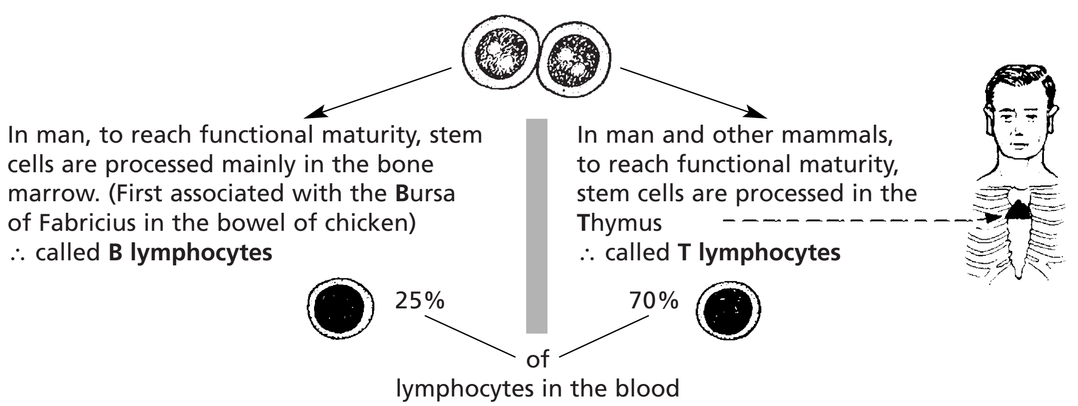
EPITOPES are the immunologically active regions of an antigen that bind to specific membrane receptors on lymphocytes or to secreted antibodies. B and T cells recognise different epitopes on the same antigenic molecule. B cells usually recognise soluble antigen (exogenous). Epitopes recognised by T cells are often internal peptides that are exposed by processing with antigen-presenting cells (endogenous).

INTER-RELATIONSHIP OF INNATE & ADAPTIVE IMMUNITY

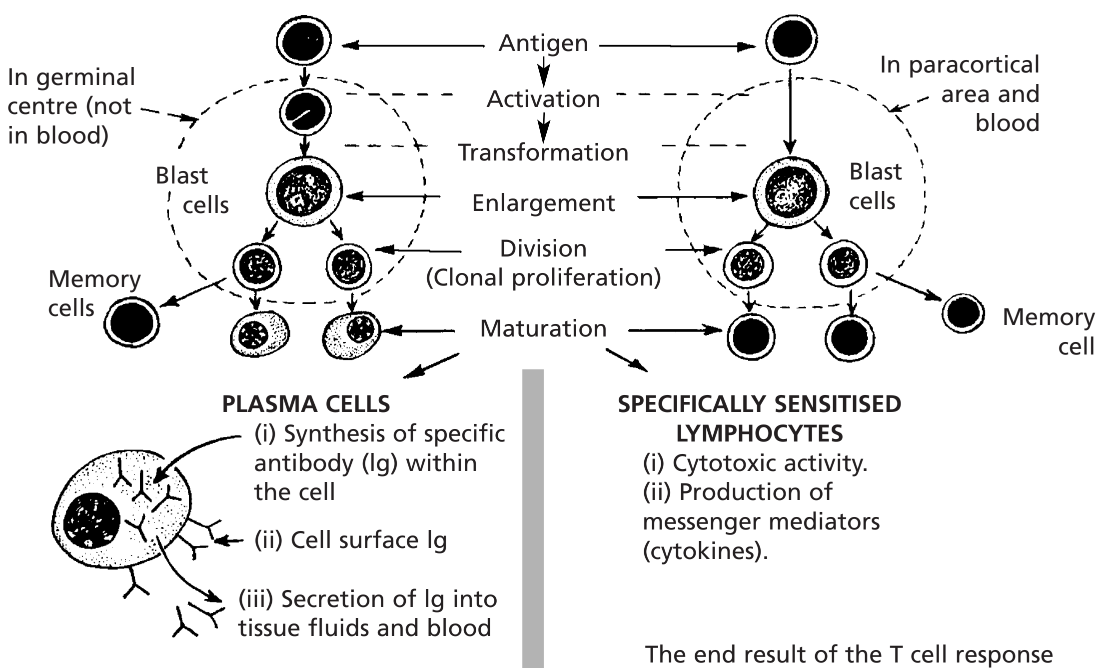


CELLULAR BASIS OF THE ADAPTIVE IMMUNE RESPONSE

The main cells of the adaptive immune response are the lymphocytes. They are indistinguishable by light microscopy using conventional stains but can be separated by the presence of different surface proteins on T and B cells.



The introduction of an antigen results in activation and proliferation of these two lymphocyte populations. This activity takes place in the lymphoid tissues.



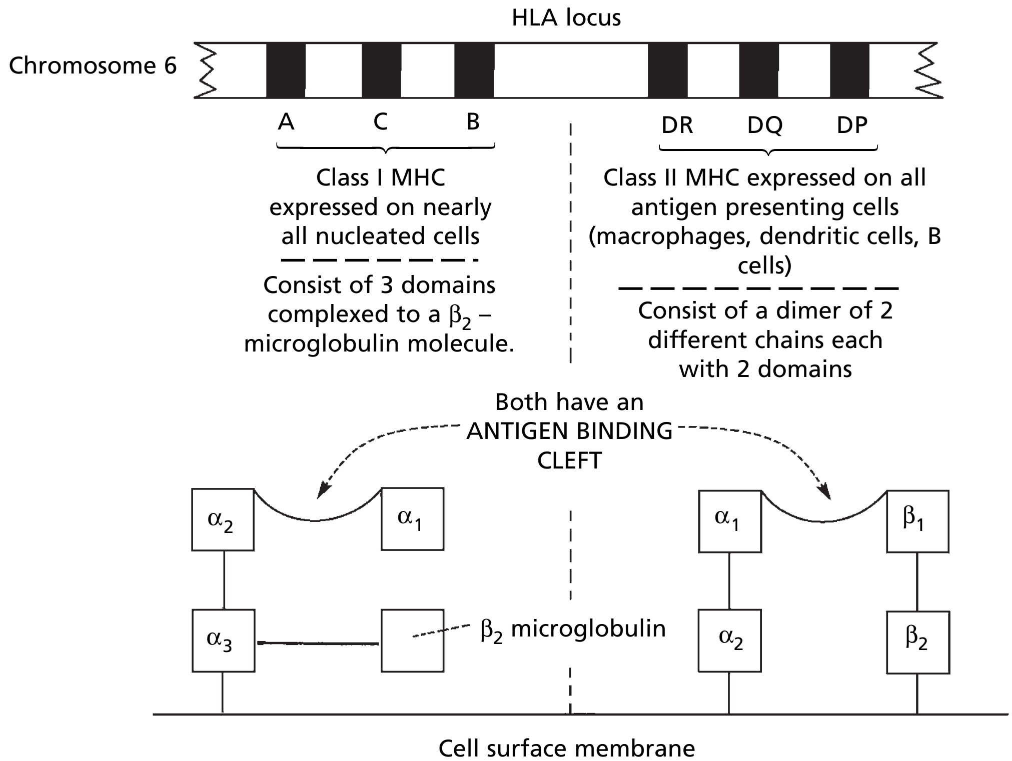
The end result of the B cell response is the formation of humoral antibodies or
HUMORAL IMMUNITY
– protection against extracellular infection.

The end result of the T cell response is the formation of
CELLULAR IMMUNITY
– protection against intracellular organisms, e.g. viruses and some bacteria (e.g. T.B.).

GENETIC INFLUENCES ON THE IMMUNE RESPONSE

The MAJOR HISTOCOMPATIBILITY complex, also known as the human leucocyte antigen (HLA), has an important role in the IMMUNE RESPONSE and DISEASE.

The genes controlling the system are in 2 major groups (Class I and Class II) on CHROMOSOME 6: each group has 3 genes which are highly polymorphic (i.e. show great variation within individual members of the same animal species). The multiple alleles of each gene encode for surface membrane glycoproteins.



The important roles of HLA are:

(i) Presentation of peptides from foreign antigens to T lymphocytes
   Class I antigens to cytotoxic T cells (normally CD8 +ve)
   Class II antigens to helper T cells (normally CD4 +ve).

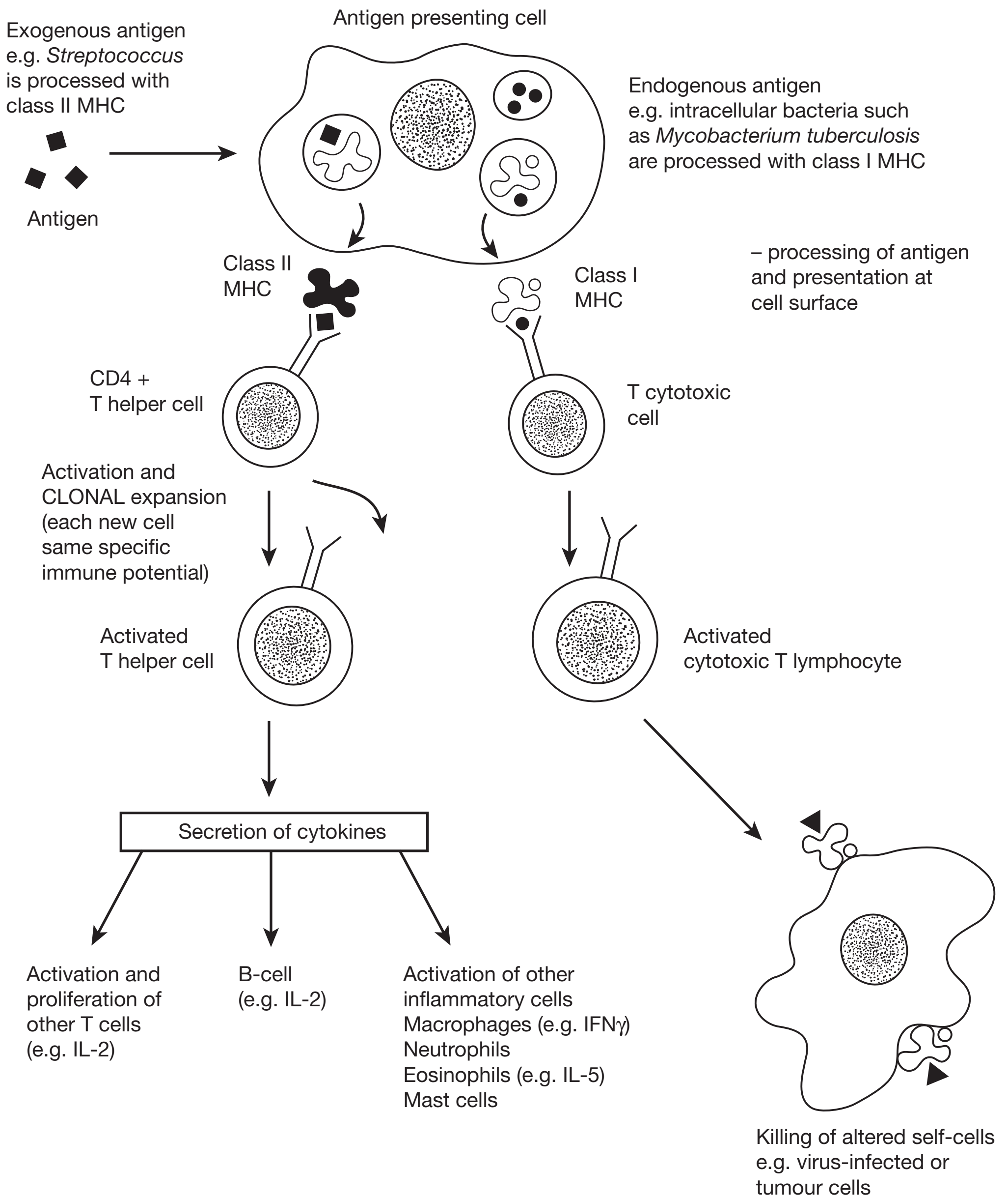
(ii) They are the main stimulus to **graft rejection** in incompatible hosts. (The better the HLA match, the better the chance of graft survival.)

(iii) There is a strong association with diseases – especially **auto-immune** disorders (p.107).
The most striking example is **ankylosing spondylitis** where >90% of patients carry the allele HLA B27.

(iv) They control individual resistance/susceptibility to certain infections, e.g. HLA B52 is associated with resistance to HIV infection.

CELLULAR IMMUNITY

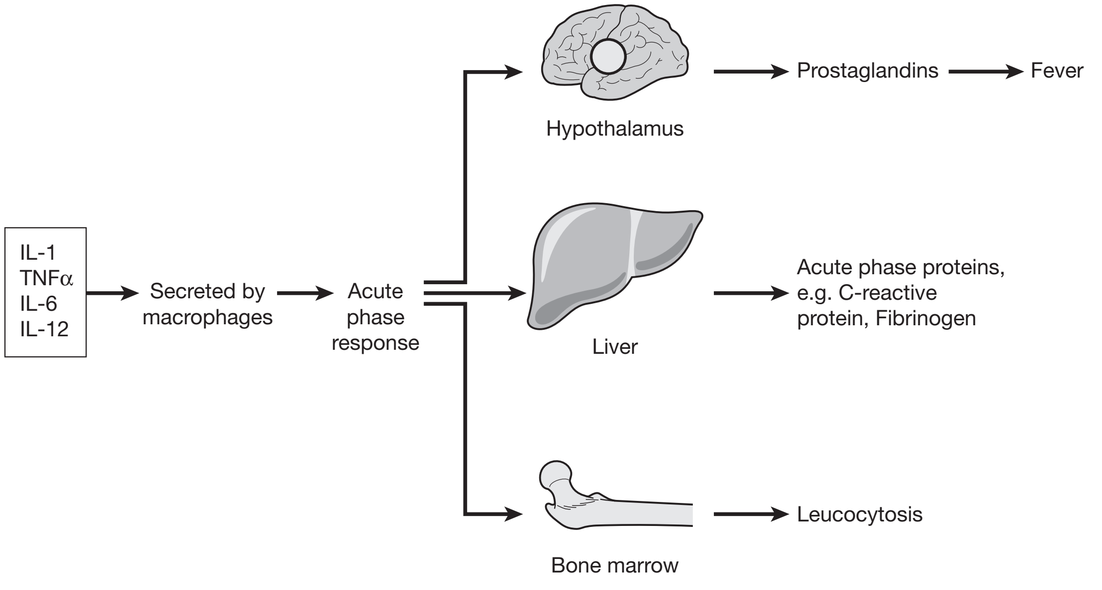
Activation of T cells requires the involvement of ANTIGEN PRESENTING CELLS. Within these cells, foreign antigen is proteolytically digested to short peptides and then presented with HLA molecules to the T cell which possesses a specific receptor for that antigen.

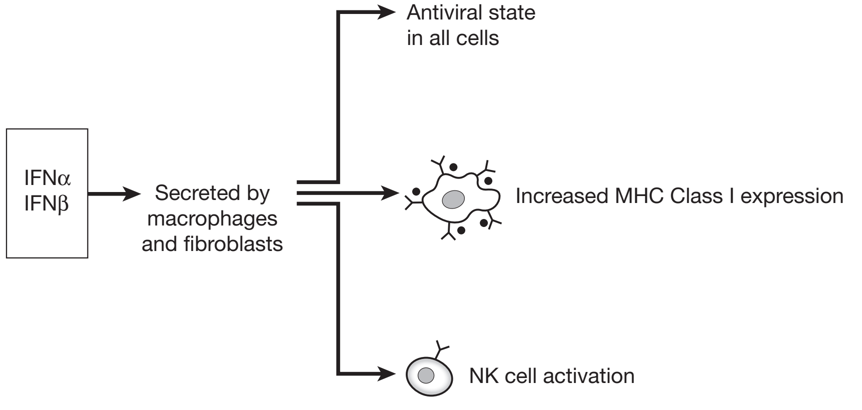


CYTOKINES

The chemical messengers of immune system are known as CYTOKINES. These small proteins are produced by virtually all cells of the innate and adaptive immune system, particularly CD4+ lymphocytes. The quantity and type of cytokine can positively and negatively regulate cells and cytokine effect is in turn controlled by expression or down-regulation of cytokine receptors on the cell surface.

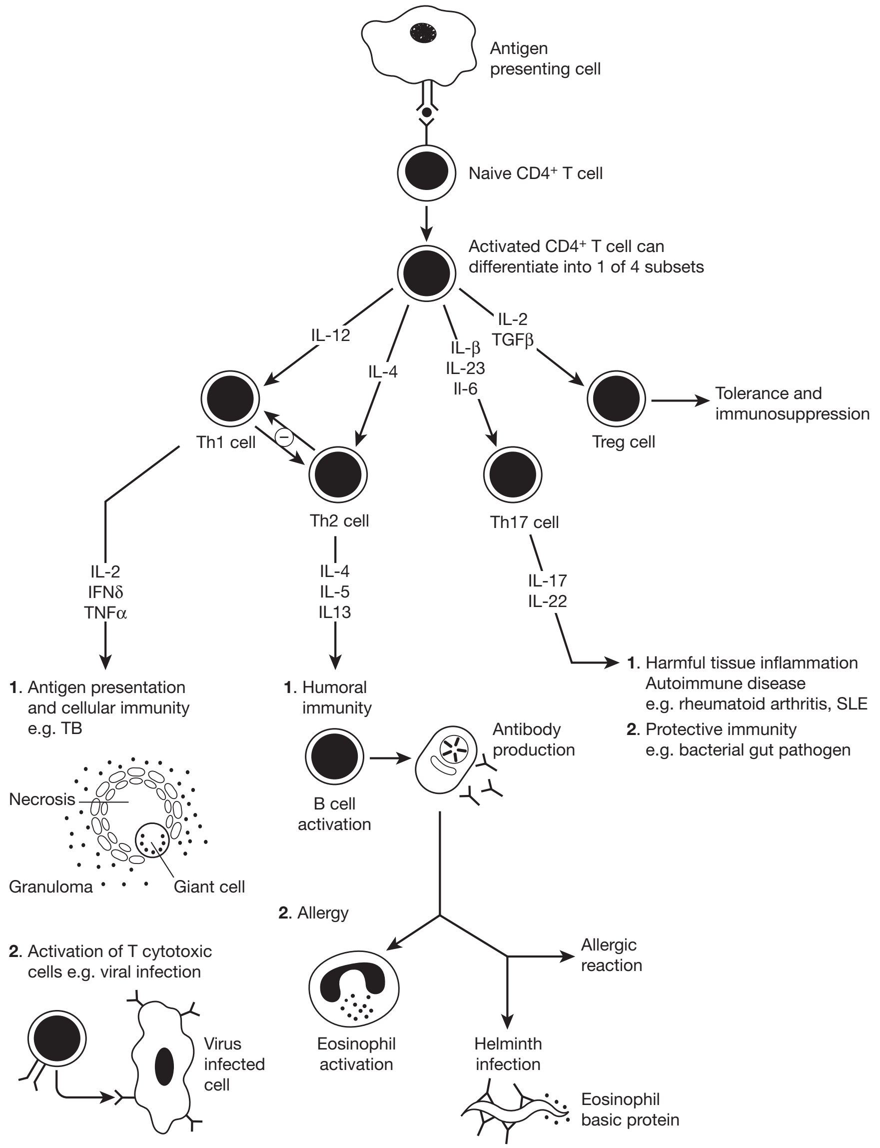
CYTOKINES INVOLVED IN INNATE IMMUNITY





CYTOKINES INVOLVED IN ADAPTIVE IMMUNITY

The immune response to a particular pathogen must induce an appropriate set of effector functions that can eliminate the pathogen from the host. Differences in cytokine secretion patterns among T helper cells are determinants of the type of immune response made to a particular antigenic challenge. Accordingly the cytokines secreting T helper cells are currently divided into 4 subsets:

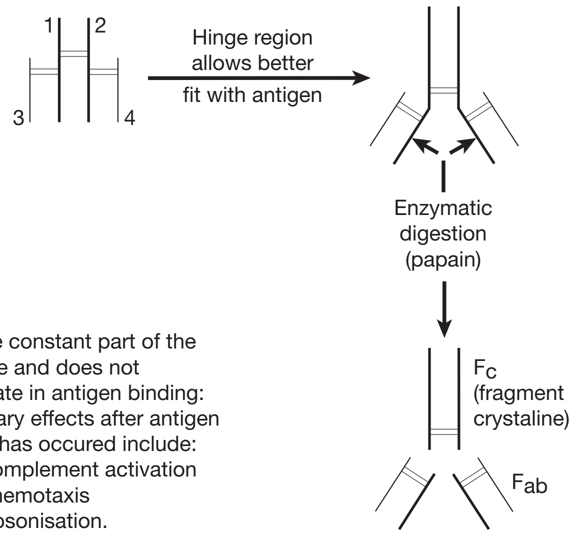


The balance between the two main subsets determines disease outcome, e.g. tuberculoid leprosy is characterised by a TH1 response (destructive granulomas, few parasites). In lepromatous leprosy there is a TH2 response (disseminated disease, many parasites).

HUMORAL IMMUNITY

BASIC STRUCTURE OF IMMUNOGLOBULIN

The basic immunoglobulin is a protein molecule consisting of 2 identical LIGHT chains and two identical HEAVY chains. Each light chain is bound to a heavy chain by a disulphide bond. Similarly disulphide bridges link the two heavy and light chain combinations to form the basic four chain structure.



F_c is the constant part of the molecule and does not participate in antigen binding: Secondary effects after antigen binding has occured include:

- complement activation
- chemotaxis
- opsonisation.

1 and 2 are heavy chains. Differences in structure allow separation of five main Ig classes – IgG; A; M; D; E. 3 and 4 are light chains. They exist in two forms – Kappa (κ) and Lambda (λ). In any one molecule both chains are either κ or λ.

F_{ab} are the variable parts of the molecule and are the site of antigen binding, the variation in amino acid content allowing a wide range of specific activity.

ANTIBODY MEDIATED EFFECTOR FUNCTIONS

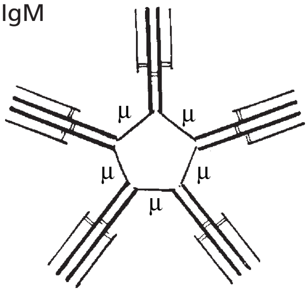
1. **Opsonisation**
   Fc receptors on macrophages and neutrophils can bind the Fc of Ig molecule resulting in phagocytosis of the antigen-antibody complex.
2. **Complement Activation**
   IgM and IgG subclasses can activate the complement system.
3. **Antibody-Dependent Cell-Mediated Cytotoxicity (ADCC)**
   The linking of antibody bound to target cells (e.g. virus infected cells) with the Fc receptors of natural killer (NK) cells, enables the NK cell to recognise and kill the target cell.
4. **Crossing of Epithelium (Transcytosis)**
   The delivery of antibody to the mucosal surfaces of the eyes, nose, mouth, bronchi and gut, as well as transport to breast milk, requires the movement of immunoglobulin across epithelium, a process called transcytosis.
5. **Activation of Mast Cells, Eosinophils, Basophils**
   This is unique to IgE (see p.102).

IMMUNOGLOBULINS

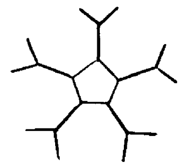
ANTIBODY CLASSES AND ACTIVITIES

These groups are named according to the composition of the heavy chains.

IgM



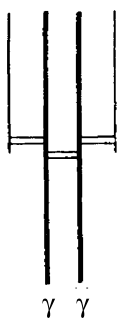
IgM (heavy chain = μ) is a polymer, joined by J chains, of five identical Ig molecules, therefore called macroglobulin. Although in low concentration in the blood, 0.5–2 mg/ml, it is the main Ig on the surface of B lymphocytes (before conversion to plasma cells). It is the first immunoglobulin class produced and is active in the primary response. It neutralises viruses. In combination with complement, it is actively bactericidal and is especially effective in bacteraemia.

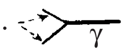


Note: The numerous (10) antigen-binding sites increase its efficiency.

The natural blood group antibodies, anti-A and anti-B are M globulins.

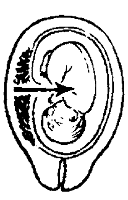
IgG



IgG (heavy chain = γ) is a single molecule with two antigen binding sites. 

This is the most abundant class of immunoglobulin, with a concentration in blood of 8–16 mg/ml. There are 4 subclasses IgG1, IgG2, IgG3 and IgG4. Of its several activities the important ones are:

1. Passive transfer of IgG (IgG1, IgG3, and IgG4) from mother to baby occurs via the placenta and colostrum. The immunity only lasts a few months.

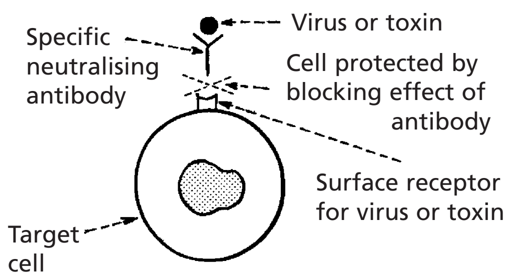


Transplacental passage of IgG



Colostrum, rich in IgG, absorbed from alimentary tract into the blood stream of the neonate

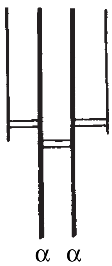
2. Neutralisation of virus and toxins.



3. Opsonisation (IgG1 and IgG3). See page 36.
4. Complement Activation (IgG3, IgG1 and IgG2). See page 99.

IMMUNOGLOBULINS

IgA

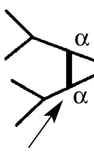


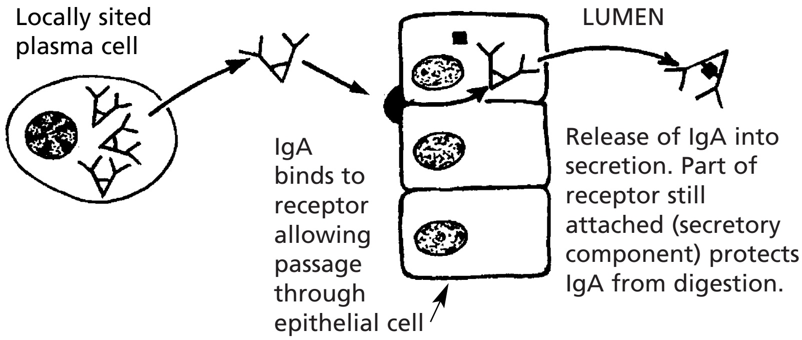
IgA (heavy chain = α) occurs in the blood (1.5–4 mg/ml) where its function is unknown.

It is the predominant immunoglobulin in secretions of eyes, nose, mouth, bronchi and gut. Its function is to protect mucous surfaces from antigenic attack and prevent access of foreign substances to the circulation and general immune system. It may neutralise toxins and prevent binding to mucous surfaces. IgA is a single molecule in the serum.

The diagram illustrates the local production of IgA in the gut.

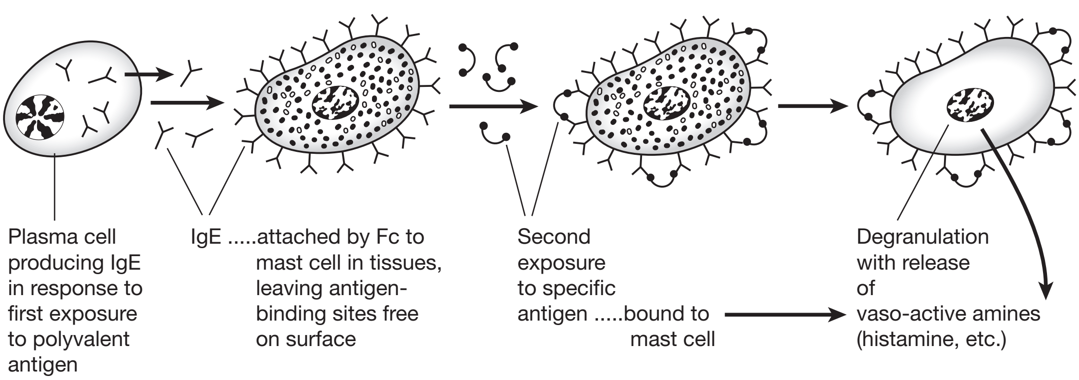
In secretions, the IgA molecule is a dimer of 2 identical molecules linked by a J (joining) chain.





IgD (heavy chain Δ) of uncertain function: concentration in blood very low probably because it is not secreted by plasma cells. Like IgM it is present on the surface of B lymphocytes prior to transformation.

IgE (heavy chain ε) – a single molecule similar to IgG and IgA. It is sometimes called REAGIN: concentration in blood is low (20–500 ng/ml). The serum level is raised in worm infestation and is probably protective. Its main activity is mediated by MAST CELLS (or BASOPHILS); it is the principal mediator of atopic and anaphylactic disease.



The range of antibodies is immense. B cells produce this vast number by rearranging the genes from the immunoglobulin light and heavy chains. The appropriate clone of plasma cells is stimulated by binding of antigen to the cell surface receptor (so-called clonal selection).

IMMUNE REACTIONS

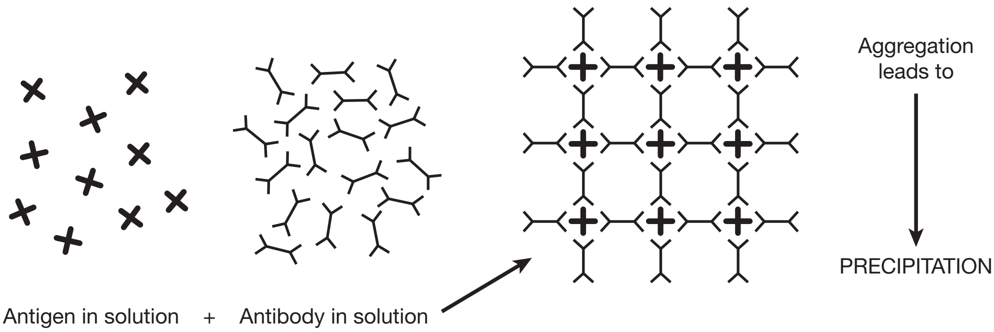
ANTIGEN-ANTIBODY INTERACTIONS

When an antigen (Ag) binds with an antibody (Ab) an Ag/Ab complex is formed. This reaction is reversible in varying degrees and depends on the **affinity** of the antibody for an individual antigen and the **avidity** (strength when multiple epitopes on an antigen interact with multiple binding sites).

The consequences of Ag/Ab interaction include:

1. **PRECIPITATION**

A soluble antigen is rendered insoluble by aggregation of the Ag/Ab complexes into a lattice.



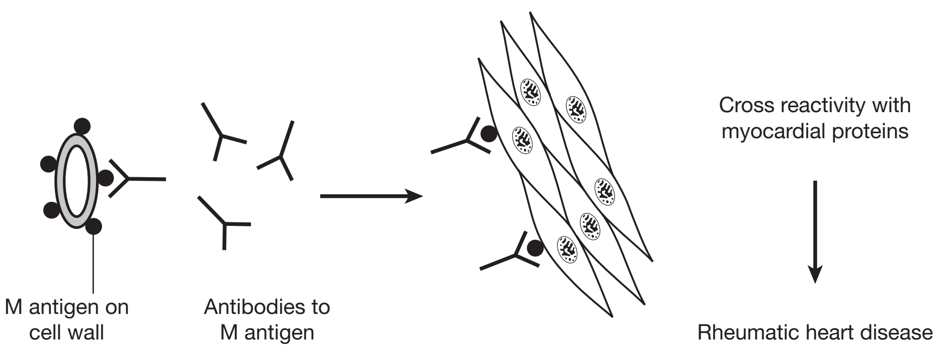
This reaction is the basis of immunoelectrophoresis, used e.g. to identify a monoclonal band in myeloma.

2. **AGGLUTINATION**

Particulate antigen, e.g. bacteria and red blood cells, are aggregated in the same way as in the precipitation reaction and the process is called AGGLUTINATION. Agglutination reactions are routinely performed to type red cells (ABO typing).

3. **CROSS-REACTIVITY**

In some cases antibody elicited by one antigen can cross-react with an unrelated antigen usually because they share a similar epitope.
e.g. Streptococcus pyogenes

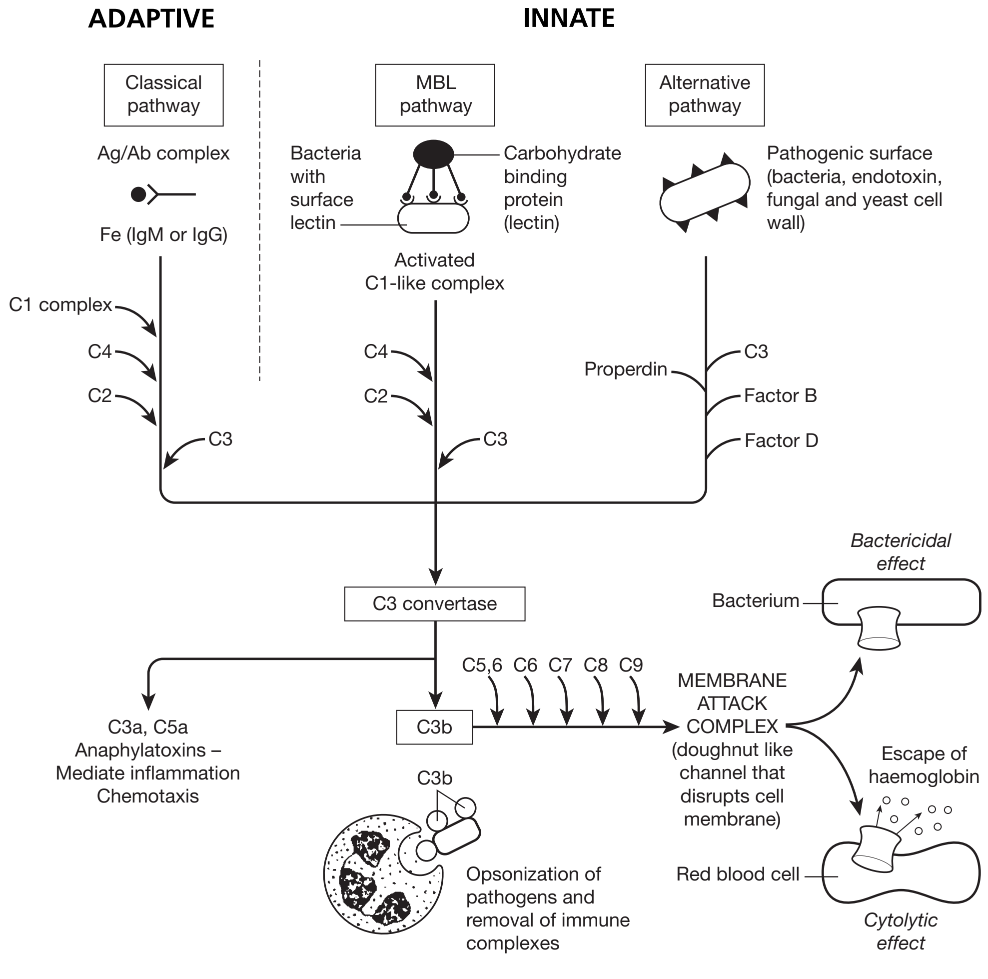


IMMUNE REACTIONS

COMPLEMENT SYSTEM

Complement consists of nine main protein components present in inactive form in the blood. There are 3 pathways of complement activation. Activation results in the formation of multi-molecular enzymes that activate further components in a cascade ultimately generating a membrane attack complex that is capable of causing cell lysis.

The mannose-binding lectin (MBL) and alternative pathways do not require antibody for activation and are therefore a component of the **innate** immune system.



Activation of C by Ag/Ab complex is called **fixation of complement.** Using red cells as markers, this fixation can detect the presence of antigen or antibody in serum.

E.g. Test serum + antigen + C.
If serum contains antibody, C is fixed, otherwise it remains free.
Add sensitised RBC (coated with Ab).
Lysis of RBC = complement still free ∴ no Ab in original serum.
No lysis = C was fixed by Ab in test serum.

TOLERANCE

Humoral and cell-mediated immunity are specific active immune responses with a protective function.

In certain circumstances an antigen does not evoke these active responses. This is because the lymphocytes, although recognising the antigen, do not react – this is TOLERANCE.

Natural 'self' tolerance
(Central Tolerance)

The immune system recognises and tolerates its own tissues.

This tolerance is developed in the fetal and early neonatal periods, and prevents autoimmune diseases in normal individuals.

Occurs in bone marrow and thymus.

SPECIFIC RECOGNITION OF ANTIGEN BY LYMPHOCYTES

↓

ABSENCE OF USUAL IMMUNE RESPONSES

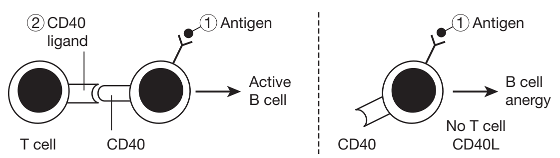
Acquired tolerance
(Peripheral Tolerance)

After the neonatal period and throughout adult life, injections of soluble foreign antigens by selected routes (e.g. I.V., mucosal) may induce tolerance in the adult.

This form of tolerance is the basis of desensitisation treatment in allergic disease and explains the absence of e.g. food hypersensitivity in normal individuals.

Occurs in mature lymphocytes.

1 **Anergy** – Both B and T cells require 2 signals for activation. Lack of the second signal switches the cell off.



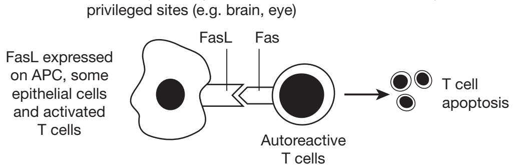
For T cells the signals are 1 MHC peptide and 2 costimulatory molecule B7.2 on APC
A third signal for T cells that provides direction has been proposed (e.g. for Th1, IL-12 and for Th2, IL-4)

2 **Deletion** – In fetal life all T and B lymphocytes that recognise 'self' antigens are eliminated by apoptosis

3 **Clonal ignorance** – Autoreactive lymphocytes may remain unactivated because they have a weak affinity for the 'self' antigen. They have the potential to be activated under certain circumstances and therefore pose a threat to the host.

4 **Receptor editing** – In this process there is secondary rearrangement of an immunoglobin variable region altering receptor specificity and averting autoimmunity

5 **Fas-FasL interactions** – Fas-mediated apoptosis plays a critical role in the removal of mature autoreactive B and T lymphocytes. Fas-mediated apoptosis plays an important role in immune privileged sites (e.g. brain, eye)



6 **Regulatory/suppressor T cells** – A specialised population of T cells that suppress the responses of other lymphocytes

Tolerance is an important protective mechanism. When it breaks down, the serious effects give rise to **autoimmune disease** (see p.107).

IMMUNOPATHOLOGY

The complicated and delicately balanced immune mechanisms clearly have been developed to protect against antigens, particularly infections. When these immune reactions are upset, the protective mechanism can itself be a source of disease states.

There are three main categories: 1. hypersensitivity states, 2. immune deficiency states and 3. autoimmune diseases.

HYPERSENSITIVITY REACTIONS

These consist of an inappropriate response by an individual to an antigen, following a previous exposure. They differ from the protective immune response in that they are exaggerated, inappropriate or damaging to the host. Depending on the main type of immune response concerned, these are classified as follows:

(a) Those associated with *HUMORAL ANTIBODIES*
∴ immediate – types I, II, III.

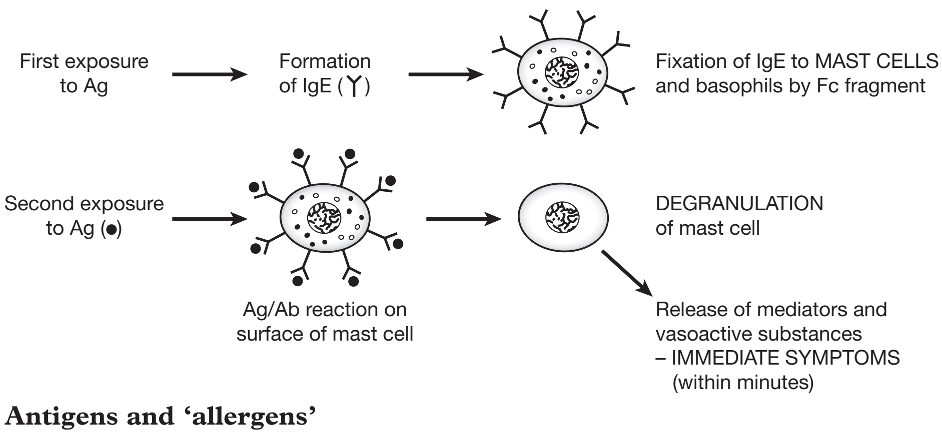
(b) Those associated with *CELLULAR IMMUNITY*
∴ delayed (24–72 hours) – type IV.

This classification is to some extent artificial. Hypersensitivity may start as an immediate humoral reaction but end in a mixed state with both humoral and cellular activities. In the 1960s, Coombs and Gell divided hypersensitivity reactions into four types that are still used today.

Type 1 Anaphylaxis, atopy, allergy

This occurs within 20–60 minutes of exposure to antigen and is often referred to as 'immediate type hypersensitivity'.

All 3 terms have been used for this reaction. The basic mechanism is as follows.



Antigens and 'allergens'

The most potent allergens are usually large molecules with molecular weights up to 40 000. Examples of common 'allergens' are pollen, house mite dust, cat fur and penicillin. Food allergy, e.g. to peanuts and milk, is uncommon.

Antibody

This is IgE. Plasma cells forming IgE are not normally found in the internal secretory surfaces of the body – tonsils, bronchi, gastrointestinal tract – but are present in large numbers in cases of allergy (and in defence against parasitic infections).

Mast cells

These have a wide distribution but are prominent in the same areas as the IgE-producing plasma cells, plus skin, bladder and synovial membranes. This explains the frequently used term 'target organs' when discussing hypersensitivity.

HYPERSENSITIVITY STATES

Clinical examples of Type I reaction

ANAPHYLACTIC SHOCK
1st injection of antigen e.g. penicillin or a bee sting → General sensitisation

---

2nd injection of above → Acute collapse: bronchial constriction; vomiting; diarrhoea; perhaps a skin rash. May be fatal. Note that the antigens are injected – enter blood stream → basophils affected → widespread reaction

HAY FEVER
1st contact with grass pollen → Local sensitisation of conjunctiva and nasal passages

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2nd contact with above → Irritation or swelling of conjunctiva with nasal excessive watery secretion

ASTHMA
1st contact with house mite dust or animal dander → Local sensitisation of bronchi

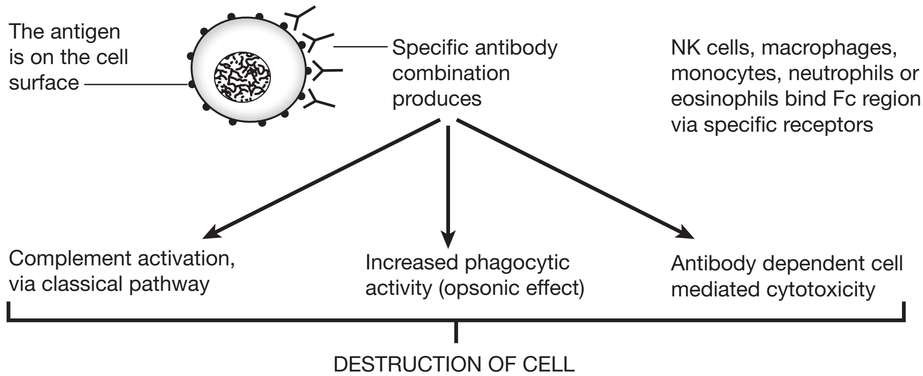
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2nd contact with above → Bronchial constriction and secretion of thick mucus cause dyspnoea (difficult breathing)

Chronic asthma may involve cellular immunity with tissue destruction.

Eosinophils are a common finding in the tissues of patients with allergies, attracted by eosinophil chemotactic factor released by mast cells. Allergic conditions are often familial with a genetic basis. Several candidate loci have been proposed including loci linked to cytokine genes and a gene for the IgE receptor on mast cells.

Type II – Cytotoxic type

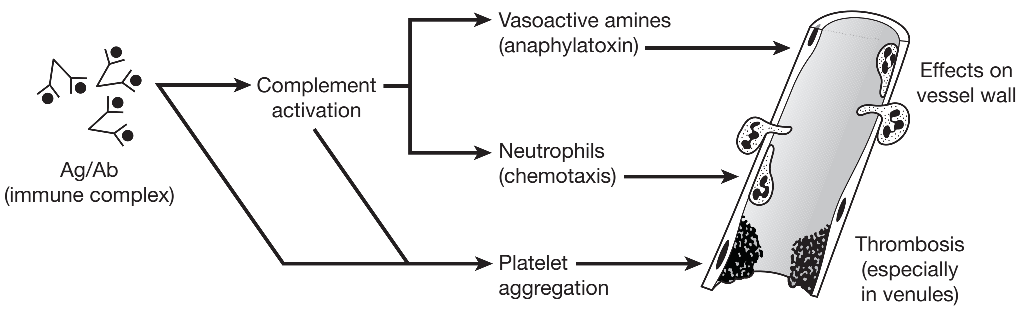


This cytotoxic reaction causes some forms of haemolytic anaemia (e.g. autoimmune HA (p.392): Rhesus incompatibility (p.393)) and some blood transfusion reactions. Certain drugs (e.g. penicillins) can also cause autoimmune HA by acting as a *hapten.* This is a small molecule that only becomes immunogenic when combined with a host protein carrier.

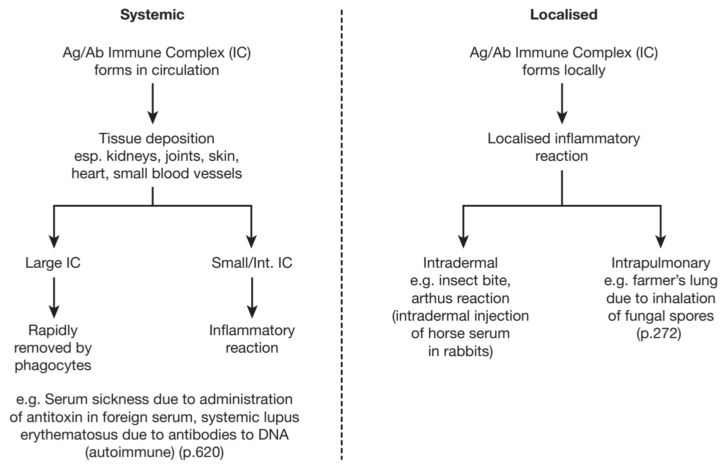
In some auto-immune disorders antibodies of this type are directed against specialised cell surface receptors, e.g. Graves' disease or myasthenia gravis (see p.109).

Type III – Immune complex (Arthus) type
The reaction is due to the consequences of specific direct antigen/antibody combination – particularly complement activation (p.99) and platelet aggregation. The antibodies involved are IgG or IgM.

HYPERSENSITIVITY STATES

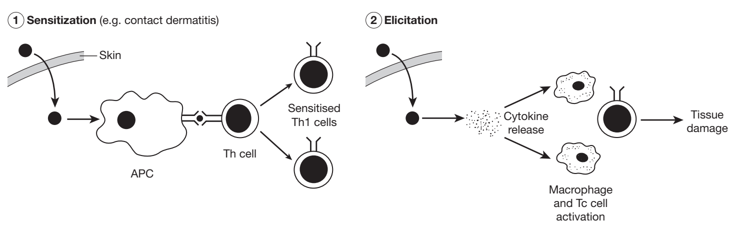


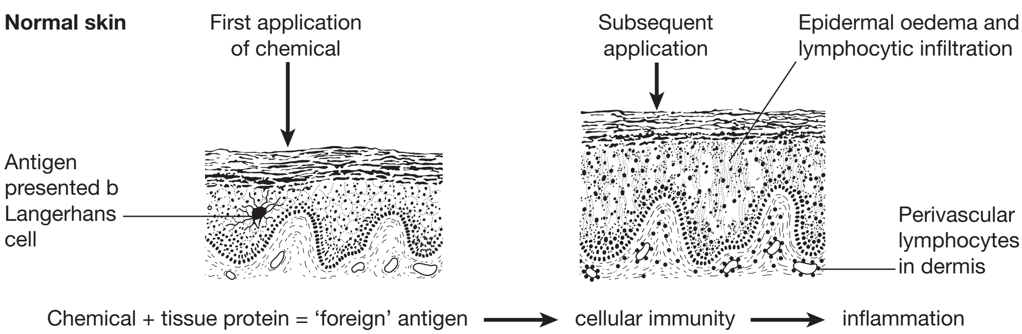
Type III hypersensitivity may be systemic or localised.



Type IV – (delayed) type

This reaction is an antigen elicited cellular immune response which produces tissue injury independently of the presence of antibody. The reaction is usually delayed taking 24–72 hours to develop. Classic examples include the tubercle follicle, graft rejection and contact dermatitis.





IMMUNE DEFICIENCY STATES

The systems involved are:

1. **THE ADAPTIVE IMMUNE SYSTEM** — humoral / cellular
2. **THE INNATE IMMUNE SYSTEM** — phagocytes / complement

Failure in any one alters the immune response. The deficiencies may be of a primary nature, commonly genetic in origin, or secondary to some other disease or circumstance. Equally, the alteration in any system may be quantitative or qualitative. In many of these deficiencies there is a failure in more than one system.

Primary (inherited) deficiencies of the specific system are rare. They include B cell, T cell and combined B and T cell deficits. B cell deficiency leads to infection by pyogenic bacteria. T cell deficits lead to infection by viruses, fungi and intracellular bacteria.

Secondary deficiencies of the specific system are common. Usually T cell activity is affected, resulting in deficient cellular immunity and, later, B cell deficit occurs.

The acquired immunodeficiency syndrome (AIDS) is now a major world-wide public health problem. Other predisposing conditions and diseases include:

Malnutrition –
particularly with protein deficiency

Iatrogenic effects –
e.g. immunosuppressors: cytotoxics, corticosteroids

Infections –
acute viral
chronic bacterial
chronic protozoal, e.g. malaria

Chronic debilitating disease –
e.g. renal failure: diabetes mellitus

Malignant disease –
e.g. advanced cancer: lymphoma, Hodgkin's disease

→ IMPAIRED IMMUNITY → INFECTION often OPPORTUNISTIC (see p.84)

Deficiencies of the innate immune system are rare. The disorders of neutrophil function are described on page 408.

IMMUNE DEFICIENCY STATES – AIDS

The acquired immune deficiency syndrome (AIDS) is a world-wide epidemic with large numbers of cases in sub-Saharan Africa and South East Asia. Globally, an estimated 40 million people are infected with the virus.

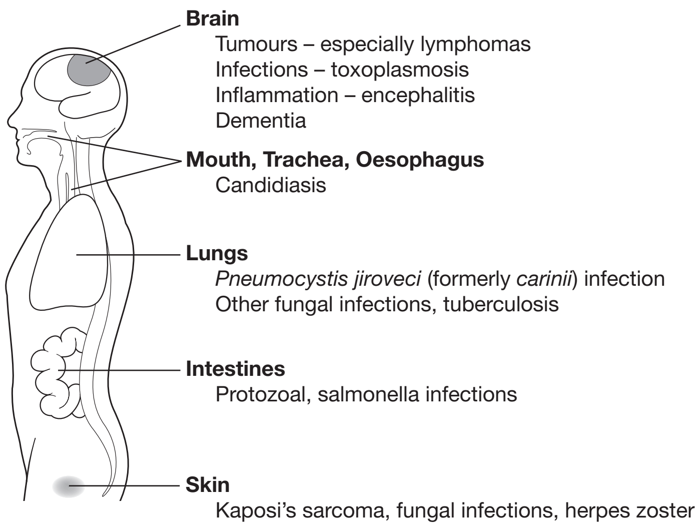
The virus (human immunodeficiency virus (HIV)) is of the retrovirus group: it infects and destroys CD4 T-lymphocytes (macrophages, monocytes and dendritic cells are also infected). There are 2 strains of HIV: HIV1 which is more virulent and HIV2 which predominates in West Africa.

The disease is slowly progressive and untreated is usually ultimately fatal. Recently highly active antiretroviral therapy (HAART), usually a combination of drugs such as nucleoside analogues and proteases, has been shown to reduce viral load to undetectable levels and has decreased the incidence of opportunistic infections and the death rate in the USA. However these drugs are expensive and have significant side effects.

Infection	Latent period	AIDS
CD4 > 500×10^6 Asymptomatic or a short febrile illness. Although the patient's cells contain HIV, tests for antibodies may be negative for up to several months.	CD4 – $200–500 \times 10^6$ Virus present in lymphocytes: may be persistent lymph node enlargement and fever.	CD4 < 200×10^6 Infections and tumours Infection – opportunistic / others Tumours – Kaposi sarcoma / lymphomas

The whole range of opportunistic infection (see p.84), including disseminated virus infection (e.g. herpes simplex and cytomegalovirus), occurs.

The diagram shows the more common AIDS-associated diseases and sites:



Blood Changes

Antibodies – Specific antibodies appear up to 6 months after infection and form the basis of the diagnostic test for HIV. The antibody titre may fall greatly late in the disease.

Immunoglobulins are usually elevated in the early stages.

CD4 lymphocytes may be severely reduced, producing a lymphopenia (see above).

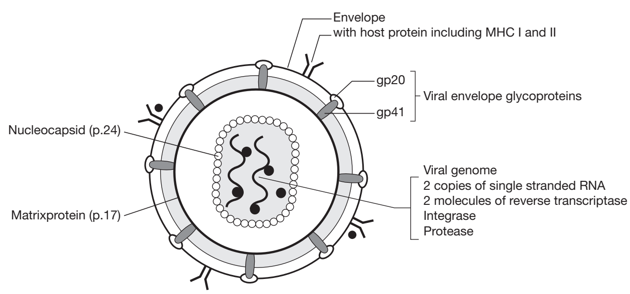
IMMUNE DEFICIENCY STATES – AIDS

EPIDEMIOLOGY AND TRANSMISSION

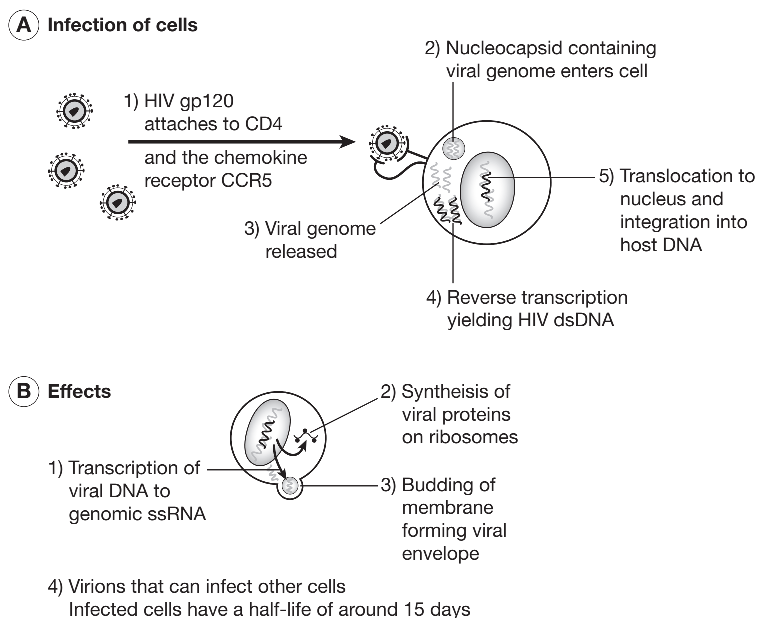
Although the virus may be present in many body fluids and secretions, transmission is by the parenteral route, usually by 1. **sexual contact,** 2. **infected blood** or 3. **from mother to infant**.
Transmission does not occur with normal social contact and there is a very low risk to medical or nursing personnel using normal procedures.

1. **Sexual contact:** HIV is present in semen and vaginal fluid. Transmission may occur by homosexual intercourse. The risk of transmission is increased where there is genital ulceration or abrasion.
2. **Infected blood:** the risk from blood transfusion and blood products has now been virtually eliminated by screening and sterilisation procedures (in the past many haemophiliacs were infected). The communal use of contaminated syringes and needles is important among drug addicts.
3. **Mother to infant:** around half a million infants become infected with HIV each year. The majority of these infections result from transmission of virus from HIV infected mothers during childbirth or by transfer of virus in milk during breastfeeding. Maternal antiretroviral therapy can reduce the incidence of transmission.

Cellular mechanisms



HIV virus



Note: Individuals with certain mutations in the CCR5 receptor are resistant to HIV. These mutations are more prevalent in Caucasian populations compared with African populations.

AUTOIMMUNE DISEASES

Autoimmune diseases result from, or are associated with, an immune response against the individual's own cells, or in some cases cell products. Although both humoral and cellular immunity are involved, it is thought that changes in the latter are of primary importance.

In autoimmunity, something occurs to destroy integrity of self tolerance. The aetiology of autoimmunity is not fully established. Potential causes include:

1. **Genetic susceptibility**
   – Genetic predisposition to autoimmune disease in family members.
   – Susceptibility to autoimmune disease may be linked to specific MHC alleles, e.g. ankylosing spondylitis HLA B27.

2. **Environmental susceptiblity**
   – Sequestered antigen – an antigen is exposed to the immune system following injury or infection, e.g. myocarditis after myocardial infarction.
   – Molecular mimicry – microbial antigens cross-react with self antigens.
   – Polyclonal activation – infectious agents can act as superantigens triggering many B and T cell clones.

3. **Other triggers of autoimmunity**
   – Hormones, e.g. SLE is more common in females and may be triggered by oestrogen.
   – Drugs – certain drugs may act as a **hapten** rendering a self antigen immunogenic.
   – T suppressor cells – loss of suppressor T cells can contribute to autoimmunity, e.g. individuals with inflammatory bowel disease and diabetes have reduced numbers of T suppressor cells.

AUTOIMMUNE DISEASES

Autoimmune diseases were traditionally classified as organ specific and non-organ specific. However, since there is some crossover between these two groups, they can be classified by the predominant effector mechanism leading to organ damage.

PREDOMINANTLY ANTIBODY-MEDIATED AUTOIMMUNE DISEASE

Autoantigen	Target Organ	Disease
Red blood cells	Red blood cells	Haemolytic anaemia
Acetylcholine receptor	Voluntary muscle	Myasthenia gravis
TSH receptor	Thyroid	Graves' disease
Nuclear constituents, e.g. DNA	Many – Kidney, skin, blood vessels, joint, heart	Systemic lupus erythematosus

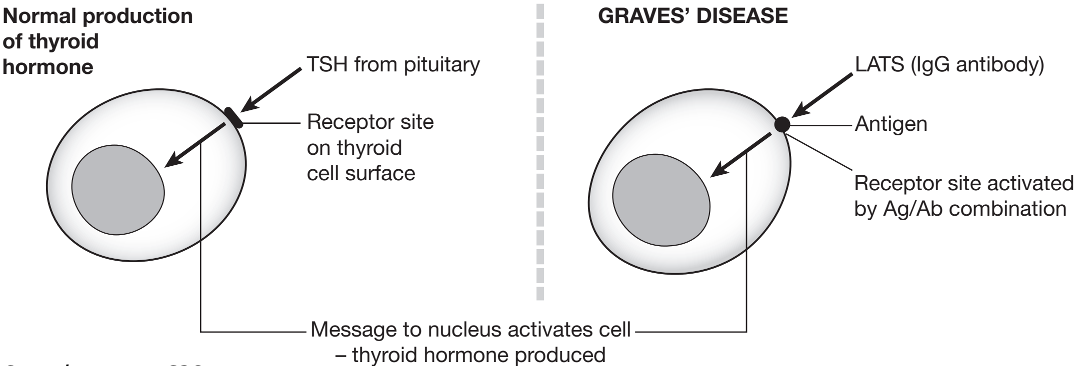
PREDOMINANTLY T CELL MEDIATED AUTOIMMUNE DISEASE

Autoantigen	Target Organ	Disease
Myelin basic protein	Central nervous system	Multiple sclerosis
β-islet cells	Pancreas	Type 1 insulin dependent diabetes mellitus
Thyroglobulin Microsomal antigens Thyroid peroxidase	Thyroid	Hashimoto's thyroiditis
IgG	Synovium/joints	Rheumatoid arthritis

AUTOIMMUNE DISEASES

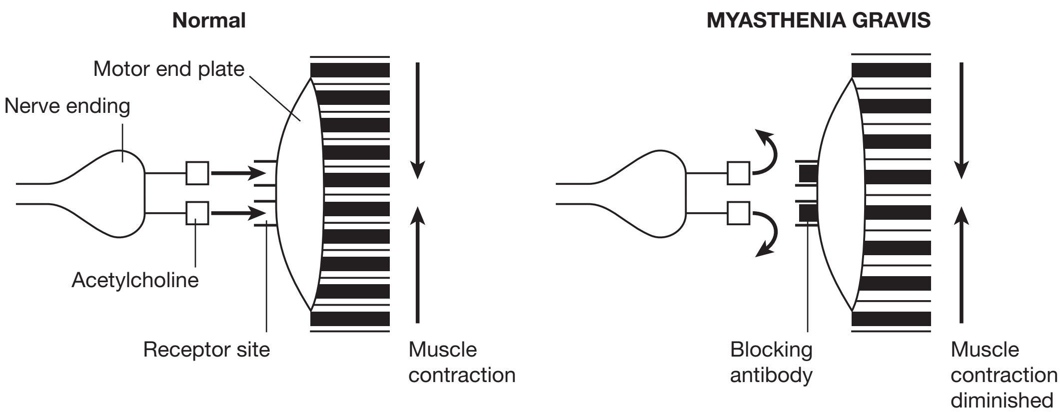
Primary thyrotoxicosis (Graves' disease) and myasthenia gravis are of particular interest. In these diseases specific autoimmune antibodies combine with antigen on the cell surface and either stimulate or block the action of the physiological agent which would normally turn on the activity of the cell.

Stimulatory effect
In Graves' disease, excessive amounts of thyroid hormone are produced. LATS (long acting thyroid stimulator), an IgG auto-antibody, combines with antigen on the thyroid cell surface and produces changes mimicking those produced by TSH (thyroid stimulating hormone) – physiologically manufactured by the pituitary.



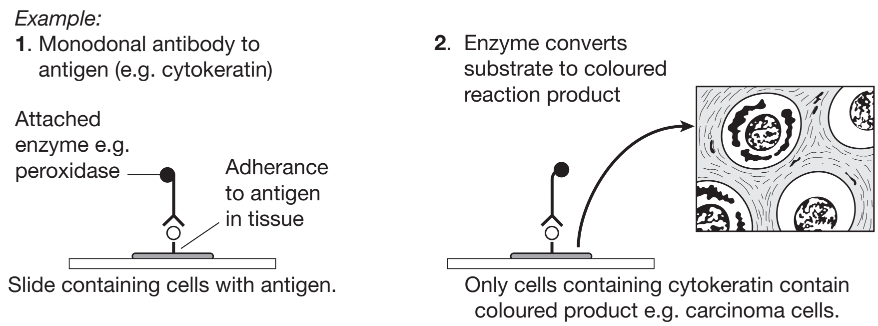
See also page 628.

Blocking effect
In myasthenia gravis, the acetylcholine formed at the motor nerve endings is prevented from stimulating the muscle motor end plate due to the antibody blocking the specific acetylcholine receptors. The end plate is also damaged (Ag/Ab + complement).



APPLIED IMMUNOLOGY

Immunohistochemical identification
Immunohistochemistry is now well established and allows identification of specific substances in histological sections.



This or similar techniques are used to identify a wide range of substances. Immunohistochemistry is now a major ancillary technique used in the pathology laboratory to subtype cancers.

Flow cytometry
In this technique, cells in suspension are labelled by fluorescent markers, excited by a laser and counted electronically by passing them through a flow cytometer. This is the technique employed, among others, for monitoring $CD4^+$ counts in HIV.

Prophylaxis and treatment of infections

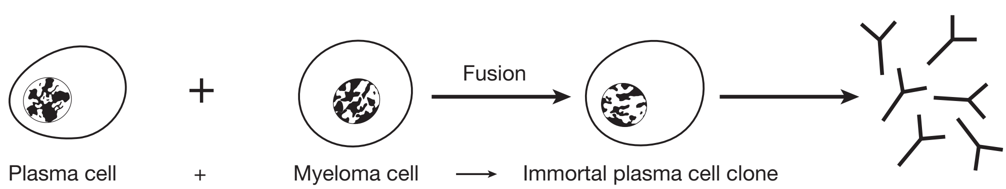
1. **Passive immunisation** is the term used when antibody formed in one individual is given to another individual who is at risk of infection — the protection is temporary. Examples include:

   Pooled human γ-globulin → general protection → particularly useful in cases of immune deficiency in agammaglobulinaemia.

2. **Active immunisation** is the term used when the infective agent is modified in some way to eliminate its harmful effects without loss of antigenicity. The subject's own immune response is activated. Examples include:

   TOXOID – e.g. tetanus toxin modified chemically.
   KILLED ORGANISMS – e.g. TAB (typhoid, paratyphoid A and B) vaccine.
   ATTENUATED ORGANISMS – e.g. viruses; cowpox, polio, measles.
   GENETICALLY ENGINEERED – e.g. hepatitis B where recombinant DNA technology is used to manufacture specific HBV proteins.

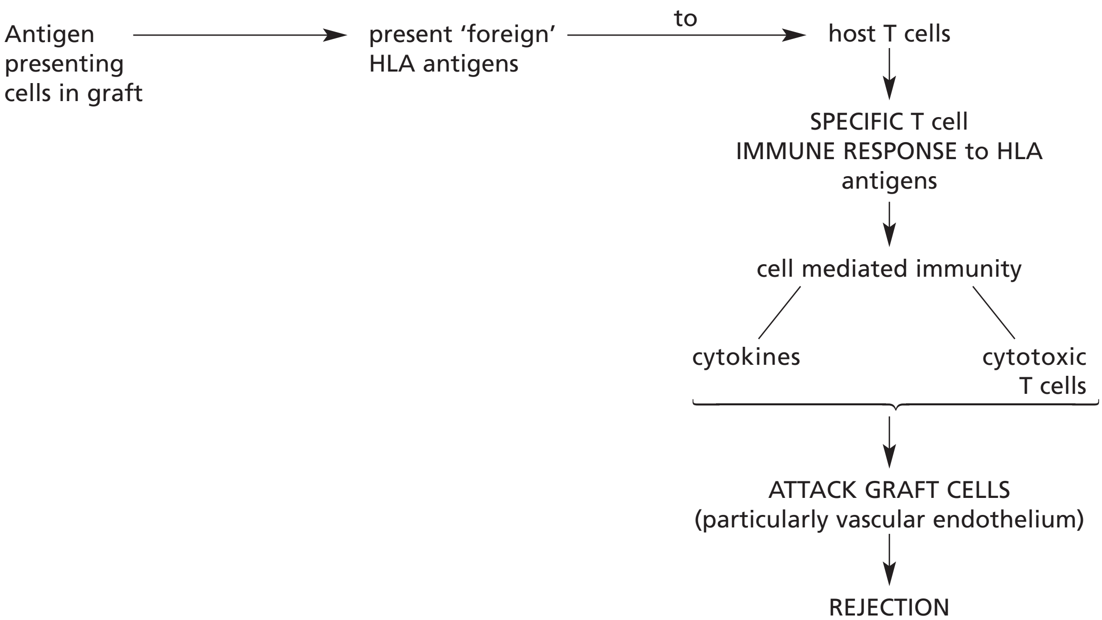
Monoclonal antibodies
These are formed by immortalising a single clone of plasma cells, by fusion with myeloma cells, so that a large amount of identical antibody is produced.



Note: Monoclonal antibodies can now be constructed from Ig gene libraries.

APPLIED IMMUNOLOGY – TISSUE TRANSPLANTATION

In the past, allografting (transplanting of tissues or organs from one individual to another of the same species) inevitably led to rejection of the graft by the host. Understanding of the mechanisms has allowed intervention so that nowadays successful survival of grafts is usual (e.g. 90% survival of renal transplants after 1 year).



Rejection may also occur, very rapidly, if pre-existing antibodies are present (e.g. due to previous incompatible blood transfusion or pregnancy) – leading to activation of complement with haemolysis.

Usually rejection takes weeks while the cell mediated immune response is building up.

The remarkable improvement in transplant prognosis is due to:

(a) careful matching of HLA compatibility between donor and recipient,
(b) use of immuno-suppressive agents (particularly cyclosporin A),
(c) screening for the presence of pre-existing HLA and cytotoxic antibodies.

Paradoxically the pre-transplant transfusion of compatible blood improves the chances of graft survival.

GRAFT versus HOST DISEASE (GvHD)
When immunosuppressed individuals (e.g. leukaemia patients) undergo bone marrow transplantation, T cells from the graft proliferate in the recipient (host) and establish an immune response against the host tissues: the main target organs are the skin, the liver and the alimentary tract.

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CHAPTER 6

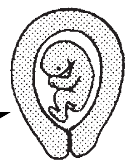
NEOPLASIA

NEOPLASIA

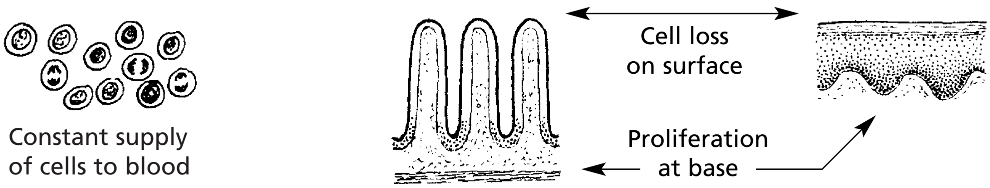
Cancer is the second commonest cause of death (25%) in the Western world after heart disease. Knowledge of non-neoplastic proliferation is helpful in understanding neoplasia.

Physiological proliferation occurs:

1. In somatic growth during fetal development.



2. In tissues where constant proliferation is needed in RAPID CELL TURNOVER from stem cells (p. 48) e.g. in:
   (a) bone marrow (b) gut epithelium (c) skin



3. Proliferation at a much slower rate occurs in tissues where cell turnover is low, e.g. LIVER, but will increase rapidly following injury.

ENLARGEMENT of an organ due to increase in the parenchymal cell mass may be due to:

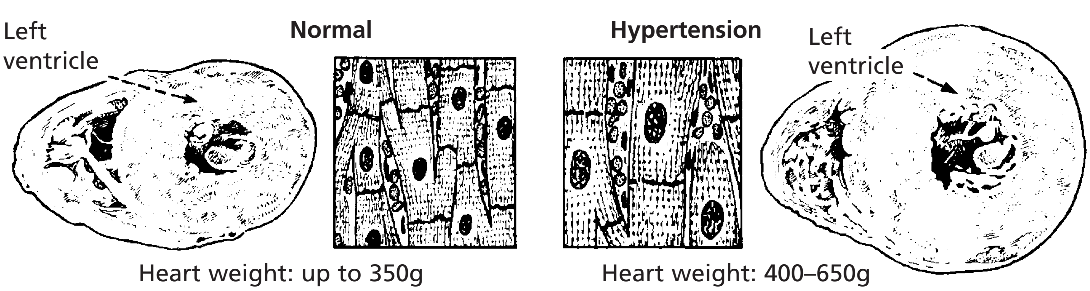
(1) an increase in the size of the individual cells – **hypertrophy**
or (2) an increase in the number of cells – **hyperplasia**
or (3) commonly a combination of (1) and (2).

The stimuli responsible are: (a) increase in functional demand
(b) increased trophic hormonal activity.

Physiological enlargement of organs is common and well illustrated by the increase in muscle bulk consequent upon training and the enlargement of uterus and breasts in pregnancy. *Pathological* enlargement is the result of disease processes.

HYPERTROPHY

Enlargement of the heart as a result of hypertension is a good example of hypertrophy: the result of the increased functional demands to maintain the high blood pressure is an increase in the size of the myocardial cells.



Heart weight: up to 350g

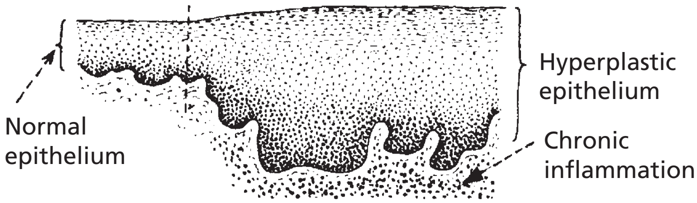
Heart weight: 400–650g due to hypertrophy of left ventricle

NON-NEOPLASTIC PROLIFERATION

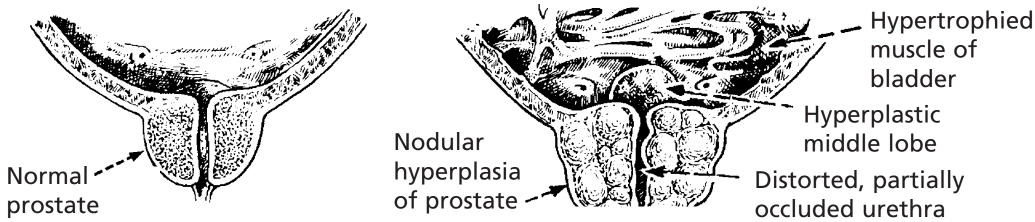
HYPERPLASIA

The two main causes are:

(a) *Chronic irritation* (and inflammation), e.g. in the skin, increased thickness results.



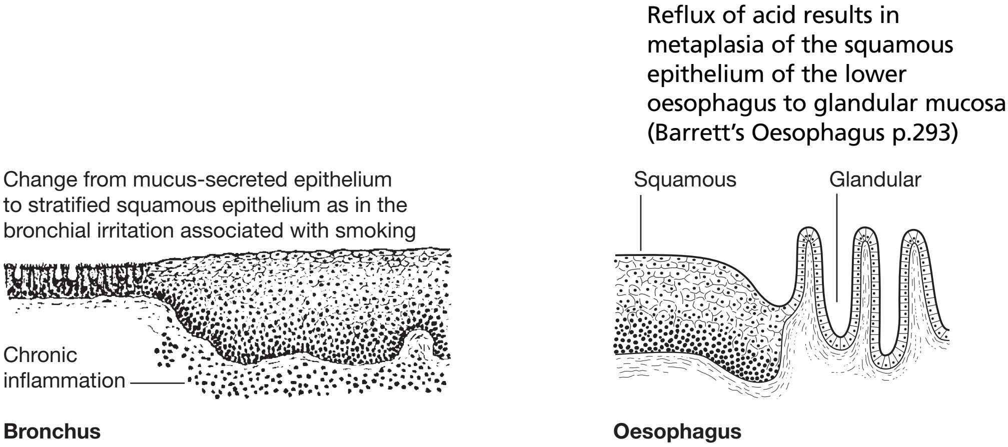
(b) *Imbalance of hormonal activity,* e.g. the irregular enlargement of the prostate in old age is due to hyperplasia of the component tissues.



Note: If the abnormal stimulus is removed, the affected organ can return to normal.

METAPLASIA

This is a change from one type of differentiated tissue to another, usually of the same broad class but often less well specialised. The change is commonly seen in lining epithelia but occurs also in connective tissues. There is frequently an associated hyperplasia.



DYSPLASIA

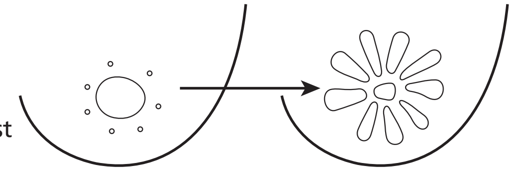
This term refers to disordered growth which is frequently the precursor of malignancy. It is described on page 145.

NEOPLASTIC PROLIFERATION

A tumour is a proliferation of cells which persists after the stimulus which initiated it has been withdrawn, i.e. it is autonomous. It is:

1. **Progressive**

e.g. Tumour of breast



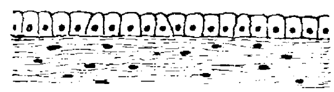
Progressive growth from few cells → large tumour.

2. **Purposeless**

e.g. Tumour of fibrous tissue



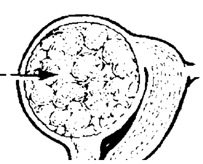
The fibres of a tumour of fibrous tissue have no regular arrangement and serve no useful purpose.



In normal fibrous tissue, the strands have a definite arrangement, supporting some structure such as an epithelial surface.

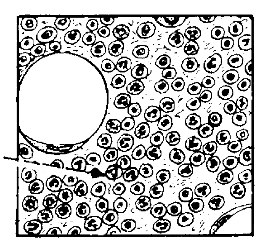
3. **Regardless of surrounding tissue**

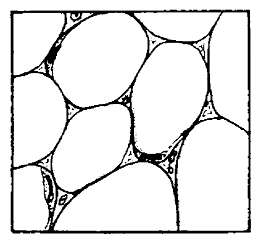
e.g. Smooth muscle tumour of uterus compresses normal tissues and distorts uterine cavity



4. **Not related to needs of the body**

e.g. In leukaemia: these tumours of bone-marrow produce needlessly, enormous numbers of leucocytes which fill the marrow, and then enter the blood stream





Normal marrow

5. **Parasitic**

The tumour draws its nourishment from the body while contributing nothing to its function. It induces the body to provide a blood supply and, in the case of epithelial tumours, a supporting stroma.

NEOPLASMS – CLASSIFICATION

Tumours may be classified in two ways: 1. clinical behaviour and 2. histological origin.

1. **CLINICAL BEHAVIOUR**

The tumour is classified according to its morbid anatomy and behaviour. Two main groups are recognised – *benign* (simple) and *malignant*. The contrast between these two groups is as follows:

	BENIGN	**MALIGNANT**
Spread (the most important feature)	Remains localised	Cells transferred via lymphatics, blood vessels, tissue planes and serous cavities to set up satellite tumours (metastases)
Rate of Growth	Usually slow	Usually rapid
Boundaries	Circumscribed, often encapsulated	Irregular, ill-defined and non-encapsulated
Relationship to surrounding tissues	Compresses normal tissue	Invades and destroys normal tissues
Effects	Produced by pressure on vessels, tubes, nerves, organs, and by excess production of substances, e.g. hormones. Removal will alleviate these	Destroys structures, causes bleeding, forms strictures

In practice, there is a spectrum of malignancy. Some tumours may grow locally and invade normal tissues but never produce metastases. Others will produce metastases only after a very considerable time while, at the other end of the spectrum, there are tumours which metastasise very early in their development.

2. **HISTOLOGICAL ORIGIN**

Tumours may arise from any tissue in the body and they can be conveniently accommodated in five groups.

1. Epithelia.
2. Mesenchymal tissues including fibrous tissue, bone, cartilage and vessels.
3. Neuroectoderm.
4. Haemopoietic and lymphoid cells.
5. Germ cells.

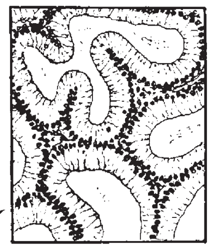
The commonest tumours arise from tissues which have a rapid turnover of cells and which are exposed to environmental mutagens, e.g. epithelium of mucous membranes, skin, breast and reproductive organs and lymphoid and haemopoietic tissues.

BENIGN TUMOURS – HISTOLOGY

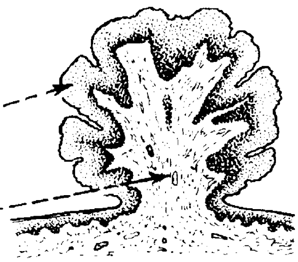
In general, the cells of benign tumours are well differentiated. They:

1. **Mimic the structure of their parent tissue.**

e.g. In an adenoma (simple gland-forming tumour) of colon the cells arrange themselves in acini.

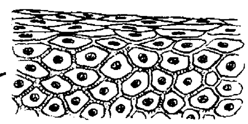


In a skin papilloma (wart) the squamous epithelium still forms a covering for underlying connective tissue

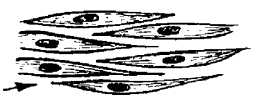


2. **Resemble the cells of their tissue of origin.**

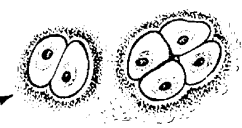
e.g. The cells of a skin papilloma are squamous



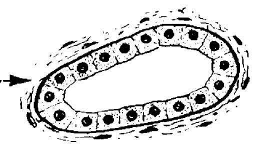
The cells of a myoma are muscle cells



The cells of a chondroma are recognisable cartilage cells



3. As in normal tissue, **show a remarkable uniformity in size, shape and nuclear configuration.**

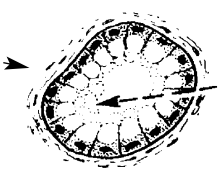


4. **Show evidence of normal function.**

This may be useless, e.g.

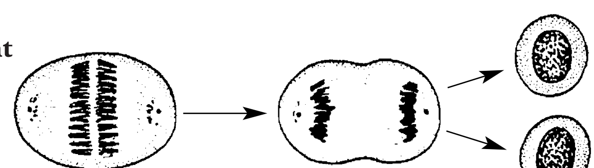
or

pathological, e.g. excess secretion of parathyroid hormone by a parathyroid adenoma.



Mucous secretion in acinus of an adenoma

5. **Have relatively infrequent mitotic figures:** these are of normal type.



Equatorial chromosomes

Division into two identical daughter cells

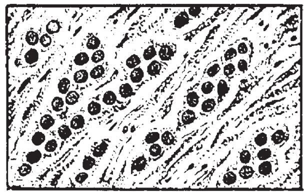
MALIGNANT TUMOURS – HISTOLOGY

The cells of malignant tumours tend to be less well-differentiated than those of benign tumours.

They:

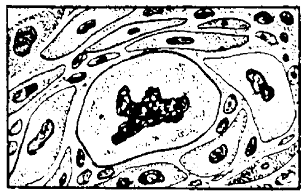
1. **Generally show a haphazard arrangement.**
2. **Bear less resemblance to the cells of origin.**

e.g. Carcinoma of breast



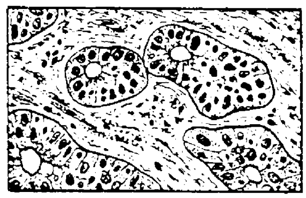
3. **Tend to vary widely in size, shape and nuclear configuration, reflecting an increase in chromosomal number and DNA content (aneuploidy).**

e.g. Pleomorphic sarcoma

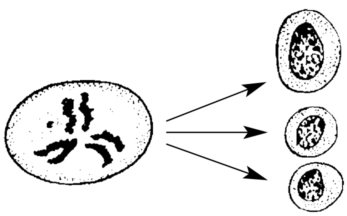


4. **Provide less evidence of normal function.**

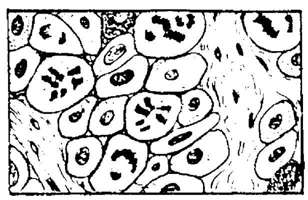
e.g. Adeno carcinoma of bowel (secretory activity limited)



5. **Show frequent mitoses often of abnormal type.**



Three daughter cells

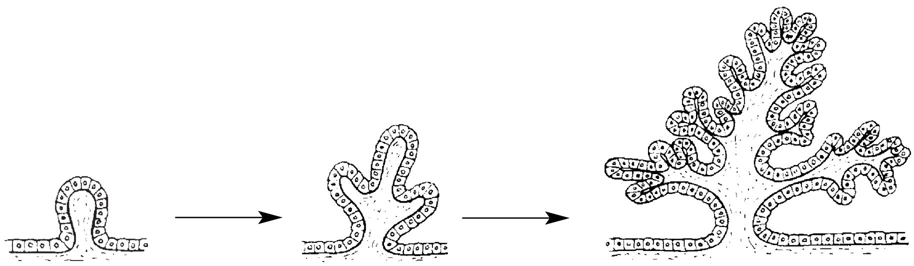


There is a spectrum within malignant neoplasms from slowly growing well differentiated examples to rapidly growing undifferentiated highly malignant tumours.

BENIGN EPITHELIAL TUMOURS

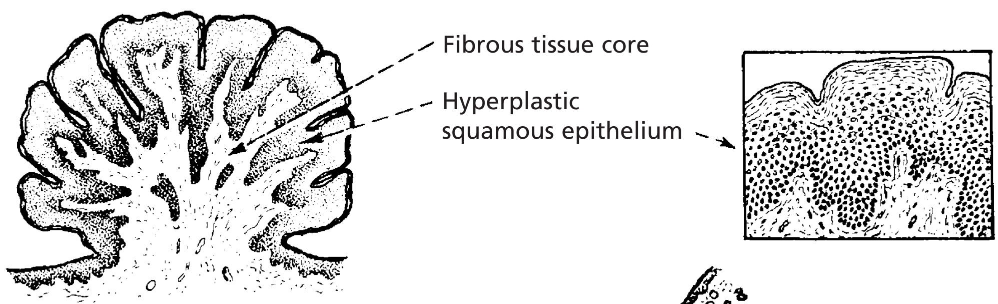
Benign epithelial tumours are essentially of two types: 1. papillomas and 2. adenomas.

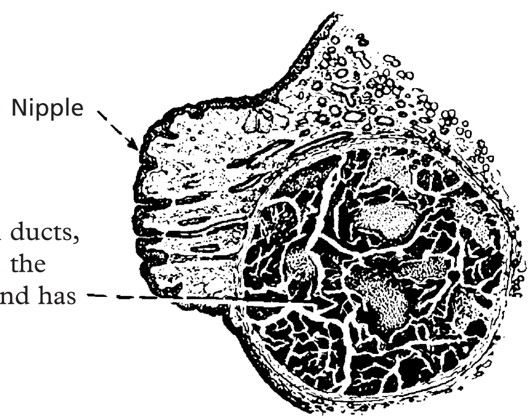
PAPILLOMA
Papillomas take origin from an epithelial surface. As the epithelium proliferates it is thrown into folds which become increasingly complex.



The epithelial proliferation is accompanied by a corresponding growth of supporting connective tissue and blood vessels.

Typical examples are found in the skin, e.g. the common wart.





Papillomas may also form within ducts, e.g. in the breast. In such a case, the papilloma is much compressed and has a complex structure.

In these benign tumours:

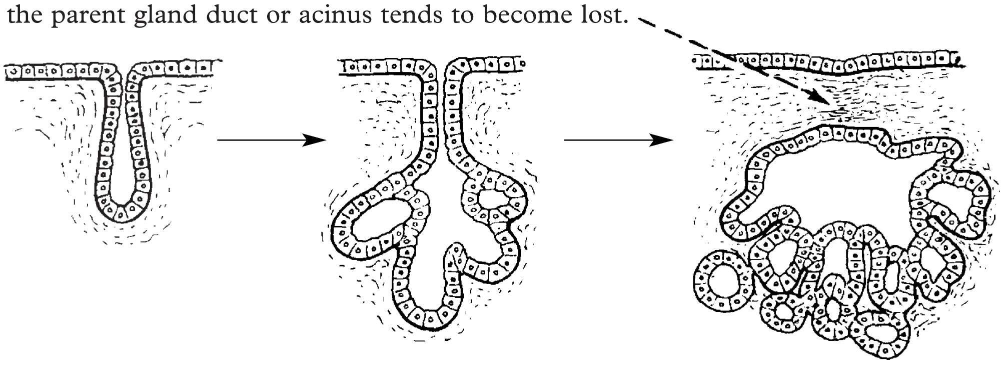
(a) The normal arrangement of epithelial cells is maintained, e.g. in skin papillomas the surface cells are squamous and proliferation is confined to the deepest layers.
(b) The relationship of epithelium to connective tissue is normal.
(c) Blood vessels are well formed.

BENIGN EPITHELIAL TUMOURS

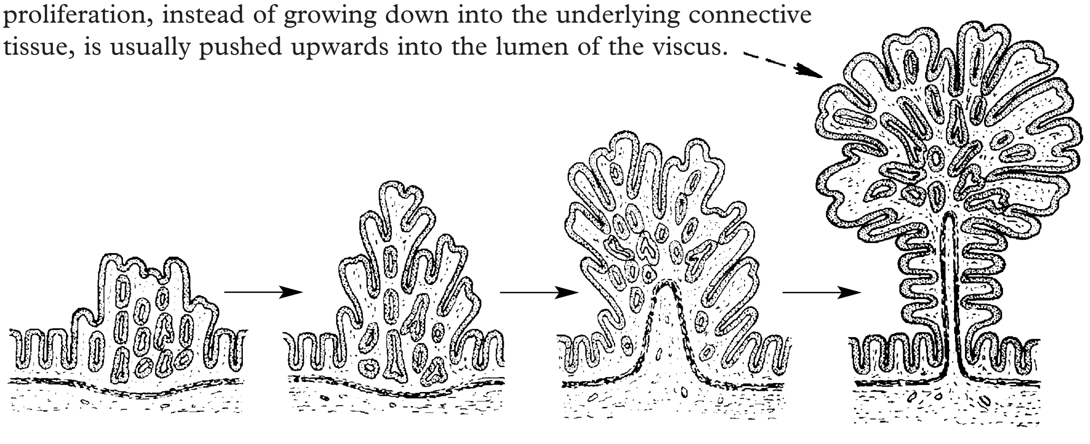
ADENOMA

Adenomas are derived from the ducts and acini of glands, although the name is also used to cover simple tumours arising in solid epithelial organs.

Again the proliferation of epithelium of a gland causes the formation of tubules which ramify and become compound. The original communication with the parent gland duct or acinus tends to become lost.



In the case of a hollow viscus, such as the intestine, the adenomatous proliferation, instead of growing down into the underlying connective tissue, is usually pushed upwards into the lumen of the viscus.



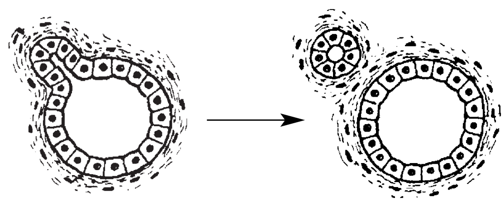
The growth therefore combines the features of a papilloma and an adenoma. The term adenomatous polyp is often applied in such a case.

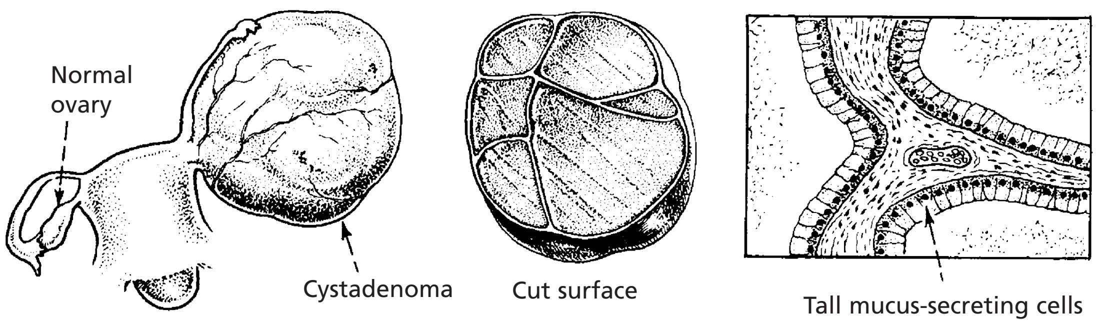
BENIGN EPITHELIAL TUMOURS

ADENOMA *(continued)*

In the type which grows into the subjacent connective tissue, the progressive budding of the epithelium results in new acini which become nipped off from the parent acini.

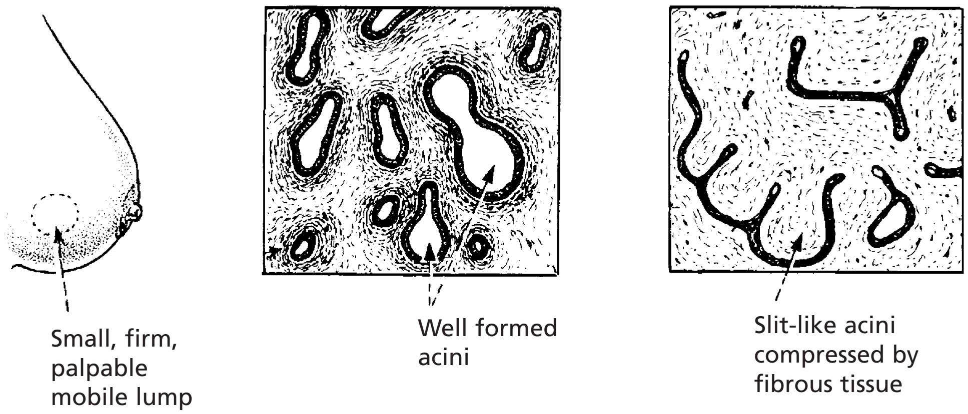
In cases in which retention of secretion is marked, a cyst forms and the tumour is then called a **CYSTADENOMA** which may reach an enormous size, e.g. some cystadenomas of the ovary may be 30–40 cm in diameter, particularly those which secrete mucus.





As in a hollow viscus, the proliferating epithelium may be heaped to form papillomas and the tumour then becomes a **PAPILLARY CYSTADENOMA**. These are also common in the ovary (see p.511).

FIBROADENOMA
In the breast the term is clinically useful for a small nodule consisting of a mixture of acinar elements and prominent supporting fibrous tissue. The histological appearances are variable depending on the distribution of the fibrous tissue (see also p.520). This is not now considered to be a true neoplasm.

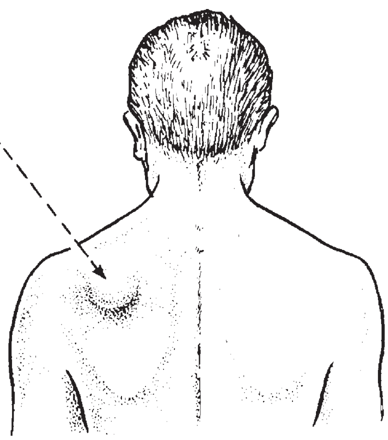


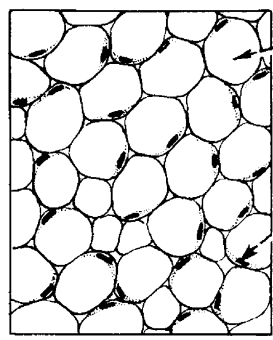
BENIGN CONNECTIVE TISSUE TUMOURS

Benign connective tissue tumours are composed of mature connective tissues – fat, cartilage, bone and blood vessels. They tend to form encapsulated rounded or lobulated masses which compress the surrounding tissues.

LIPOMA

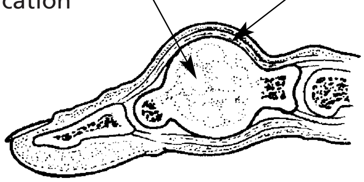
Circumscribed masses of fat are commonly found in the subcutaneous tissue of the arms, shoulders and buttocks. Less commonly they occur in the deep soft tissues of the limbs or retroperitoneum, but at these sites they must be carefully distinguished from low grade liposarcomas. Lipomas very rarely arise from the viscera.

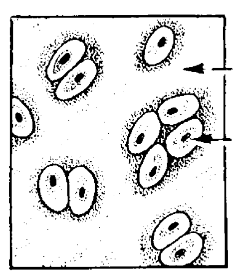




CHONDROMA

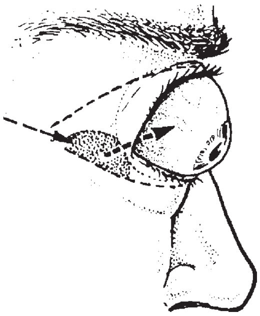
A chondroma usually arises within the medullary cavity of the tubular bones of the hands and feet; it grows slowly, causing gradual expansion of the bone. Less commonly it occurs in long bones. Rarely multiple enchondromas appear in children and are associated with deformity: they occasionally become malignant.



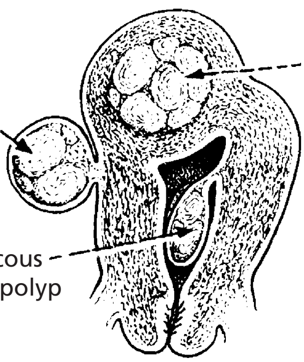


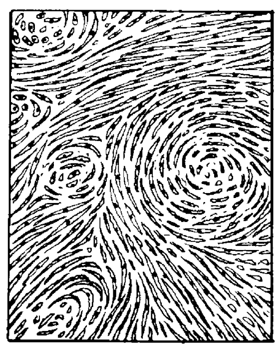
BENIGN CONNECTIVE TISSUE TUMOURS

OSTEOMA
This tumour is mainly found in the bones of the skull, although it may occur in long bones. Osteomas are relatively small but may produce severe symptoms because of their situation.



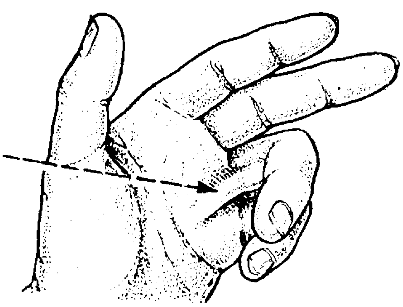
LEIOMYOMA (FIBROID)
The majority of benign smooth muscle tumours occur in the wall of the uterus where they are extremely common, but may lie within the uterine cavity or attached to the serosa. They are firm, rounded masses which usually begin in the myometrium.





TUMOURS OF FIBROUS TISSUE
So-called fibromas are rare but tumour-like growths are fairly common. An example is a FIBROMATOSIS.

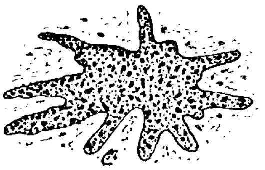
Palmar fibromatosis, at first nodular, causes flexion deformities of fingers (Dupuytren's contracture) due to contraction of fibrous tissue within the palmar fascia. A similar condition may affect the plantar fascia. Deeply located fibromatoses behave in a locally aggressive manner.



Benign tumours of PERIPHERAL NERVE and of VESSELS are described on pages 579 and 580.

MALIGNANT EPITHELIAL TUMOURS

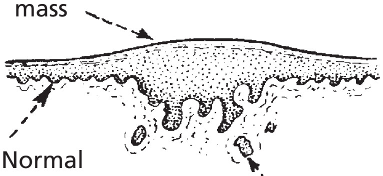
Malignant epithelial tumours are known as **CARCINOMAS** (Greek '*karkinos*': a crab), referring to the typical irregular jagged shape. This is due to invasion into adjacent normal tissues (p.135).



Types of CARCINOMA
Like benign epithelial tumours, carcinomas can arise from squamous or glandular epithelium.

SQUAMOUS CELL CARCINOMA
This is commonly found on the skin, especially exposed surfaces, but also develops in other sites covered by stratified squamous epithelium, e.g. lips, tongue, pharynx, oesophagus and vagina. In addition, it may occur on surfaces covered by glandular type epithelium through metaplastic transformation as in the bronchus, gall bladder and uterine cervix. It frequently arises from areas of carcinoma-in-situ (p.144).

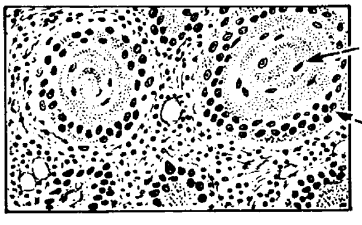
1. It starts as a small papular mass



2. The surface breaks down and a characteristic irregular ulcer is produced.



Histologically, it is composed of irregular strands and columns of invading epithelium which infiltrate the underlying connective tissue. If well differentiated, the central cells of the invading masses show conversion into eosinophilic keratin, while the outer layer consists of young basophilic cells. In cross-section, the appearance is typical.



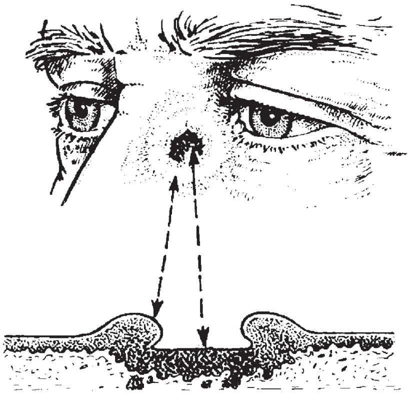
Squamous carcinoma of skin is typically well differentiated and slow growing. In contrast, uterine cervical carcinomas are poorly differentiated and spread early to draining lymph nodes.

TYPES OF CARCINOMA

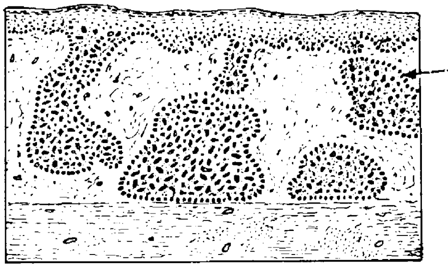
BASAL CELL CARCINOMA (Rodent ulcer)
This tumour may arise in any part of the skin but is most common in the face, near the eyes and nose.

First stage
It starts as a flattened papilloma which slowly enlarges over months or perhaps a year or two.

Second stage
The surface breaks down and a shallow, ragged ulcer with pearly edges is formed.



Usually the malignant tissue spreads slowly but progressively, mainly in a lateral direction. It is composed of cells resembling those of the basal layer of the skin; it has a characteristic histological appearance.



There are many histological variants. Sometimes they show pseudoglandular structures: melanin deposition occurs in some tumours.

Basal cell carcinoma is a locally invasive growth which can be extremely destructive (hence its name: Rodent ulcer). It almost never metastasises. Thus the two processes of local invasion and distant metastases are not necessarily linked.

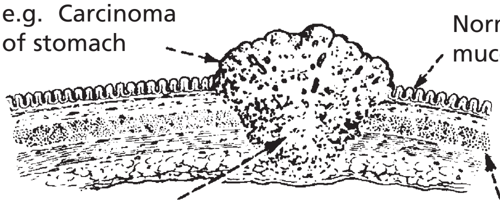
TYPES OF CARCINOMA

CARCINOMA OF GLANDULAR ORGANS

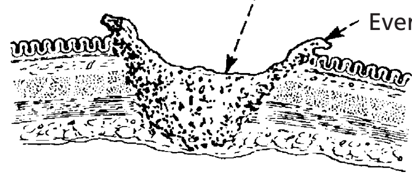
These may take origin from gland acini, ducts or the glandular epithelium of mucous surfaces. The anatomical structure varies.

(a) On mucous surfaces they may start as a polypoid growth or as a thick plaque.

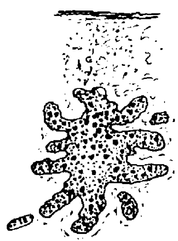
e.g. Carcinoma of stomach



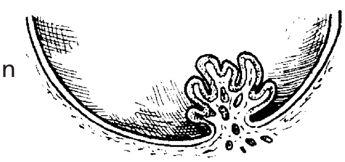
Ulceration with the formation of an irregular crater follows.



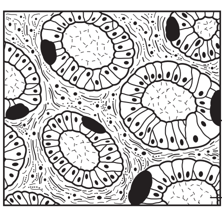
(b) In compound glands, e.g. the breast, the cancer forms an irregular penetrating mass – the typical crablike appearance.



(c) Some malignant tumours are cystic and may develop as papillomatous structures within the cyst.



Histologically, carcinomas of glandular tissue have three basic forms.

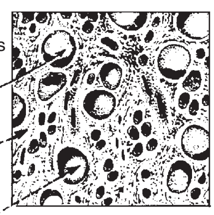


1

Adenocarcinoma: the tumour cells usually form gland-like structures.

Nucleus

Intracellular mucus



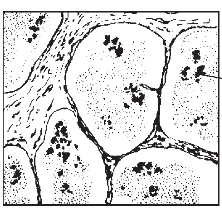
2

Typically seen in linitis plastica. These tumours consist of **signet ring cells.**

Extracellular mucin may also be present.

Globules of mucin push the nucleus to one side.

The individual cells may form intracellular gland-like structures. The resulting cell is known as a signet ring cell.
– this is commonly seen in the stomach.



3

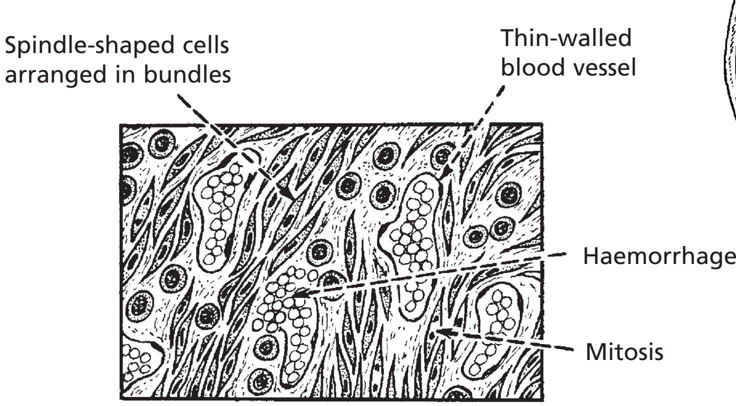
Occasionally a carcinoma will produce large quantities of mucus and merit the term mucoid carcinoma.
The tumours consist of only a few carcinoma cells in large lakes of mucus. They are commonest in organs normally containing large numbers of mucus-secreting cells, e.g. large intestine and stomach, but may also occur in the breast.

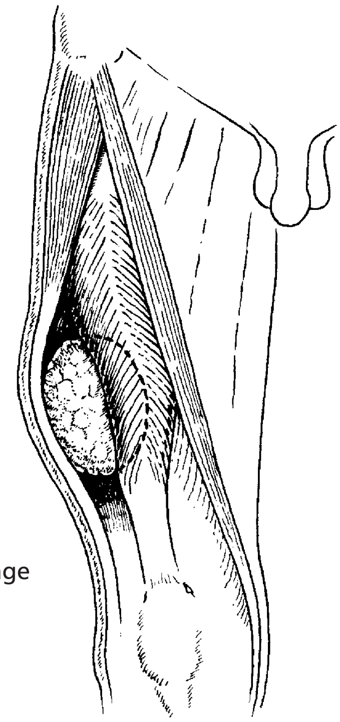
MALIGNANT CONNECTIVE TISSUE TUMOURS

Malignant connective tissue tumours are referred to as Sarcomas (Greek '*sarkoma*': flesh). They arise in soft tissue, in bone and rarely in viscera.

Sarcomas are far less common than carcinomas, but are second in frequency to leukaemias and lymphomas in childhood and early adult life.

Unlike the ill-defined infiltrative carcinomas, sarcomas are large well defined fleshy tumours. Naked eye assessment suggests that they are encapsulated, but histology shows that this is a false impression. Malignant cells do infiltrate between normal tissues at the margin, so that surgical 'shelling out' is almost inevitably followed by local recurrence from aggregates of cells remaining in the tumour bed.





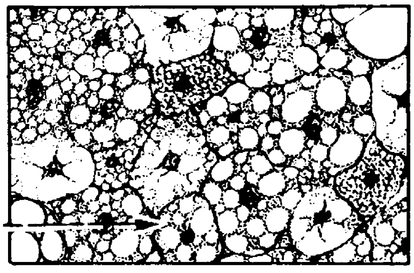
Most sarcomas consist of spindle shaped cells, although some are of round cell type. They are associated with the formation of many large thin walled blood vessels which are easily invaded by sarcoma cells. Blood borne metastases to lung are common. In contrast, lymph node involvement is rare in most types of sarcoma.

SARCOMAS

Many different histological types of sarcoma have been described. The nomenclature is based on adding the suffix 'sarcoma' to the type of differentiation shown, e.g. chondrosarcoma, liposarcoma, leiomyosarcoma (cartilage, adipose tissue, smooth muscle).

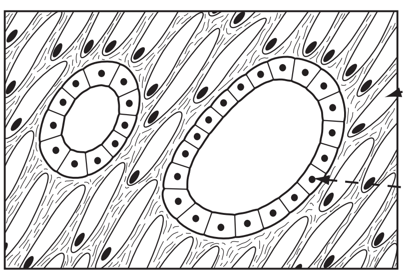
In general, the grade of the tumour is of more prognostic importance than the precise histological type. Some of the commoner forms of sarcoma are described.

Liposarcoma
This tumour arises in soft tissues of the limbs and retroperitoneum. A number of sub types are described. Primitive fat containing cells (lipoblasts) are a feature.



Well differentiated liposarcoma has a good prognosis and rarely metastasises. Pleomorphic and round cell liposarcomas are highly aggressive tumours which metastasise early.

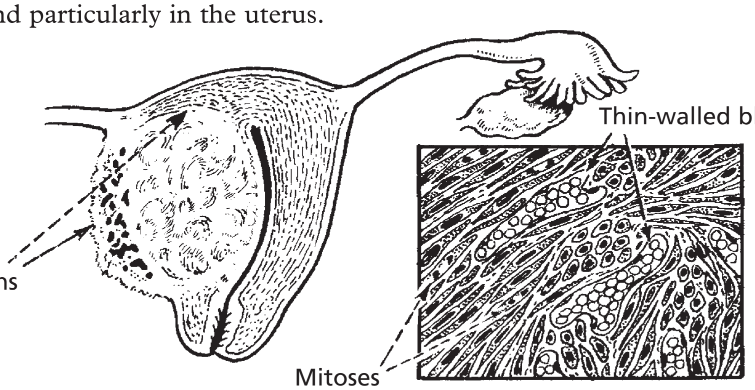
Synovial sarcoma
Although a misnomer as the tumour does not arise from synovium, this has a typical microscopic appearance. Many tumours are biphasic – with both epithelioid and spindled forms.



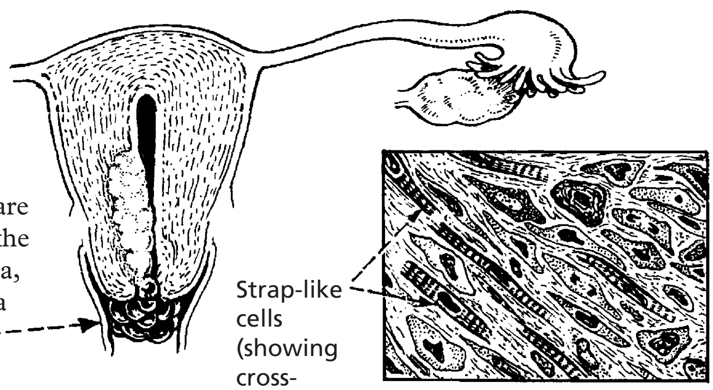
SARCOMAS

MYOSARCOMA (Sarcoma of muscle)
There are two varieties:

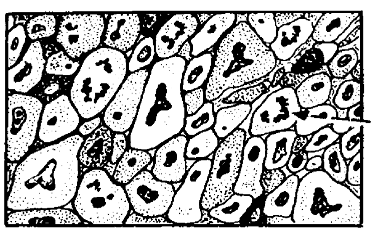
1. **Leiomyosarcoma**
   These rare tumours arise in the skin, deep soft tissues and particularly in the uterus.



2. **Rhabdomyosarcoma**
   This is a rare tumour occurring mainly in children. It occurs very rarely in skeletal muscles. More common but still rare are polypoid tumours in the bladder, uterus and vagina, sometimes called sarcoma botryoides (grape-like).



Pleomorphic or anaplastic sarcoma
Many highly malignant sarcomas are so poorly differentiated that their specific type cannot be determined.



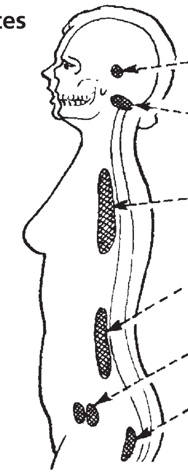
Immunocytochemistry, electron microscopy and cytogenetic analysis (demonstrating typical chromosome translocations) all help in reaching more specific diagnoses than can be reached by conventional histology alone.

Sarcomas of bone are described on page 598.

OTHER TUMOUR TYPES

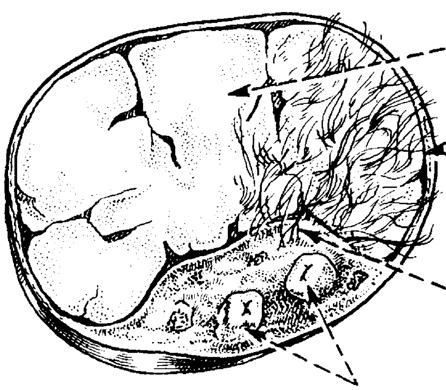
TERATOMA

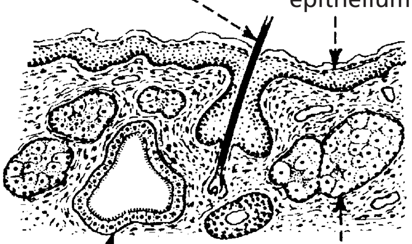
This is a tumour derived from totipotent germ cells. Most arise in the **ovary** (**usually benign**) and **testis** (**almost always malignant**): they may also occur at any site in the mid-line where germ cells have stopped in their migration to the gonads.



For example, **Benign cystic teratoma** is typically seen in the ovary.

It consists mainly of ectodermal structures such as skin and its appendages and neural tissue. Frequently respiratory epithelium, intestinal epithelium, bone and cartilage are present.





Testicular Teratomas are described on page 489.

OTHER TUMOUR TYPES

HAMARTOMA

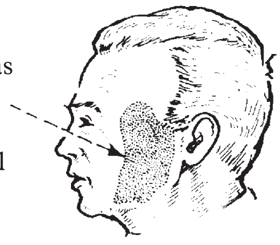
A hamartoma is a tumour-like but non-neoplastic malformation consisting of a mixture of tissues normally found at the particular site.

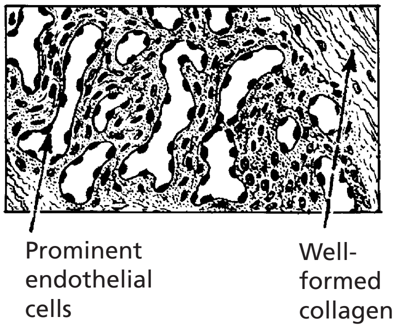
HAEMANGIOMA

Two main varieties exist:

1. **Capillary angioma**

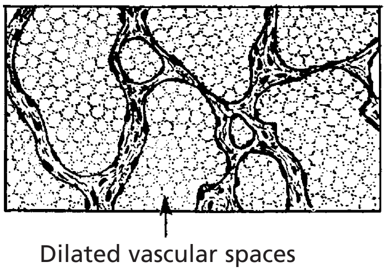
These are common in the skin as 'birth-marks' which vary in size. Occasionally they may be found in internal organs. They are well defined, deep red or purple. A single artery provides a supply separate from the surrounding tissue.





2. **Cavernous angioma**

This type is usually confined to internal organs and quite often found in the liver. Like the capillary variety they are well defined and deep purple. Similar tumours are found involving the lymphatic system but less commonly.

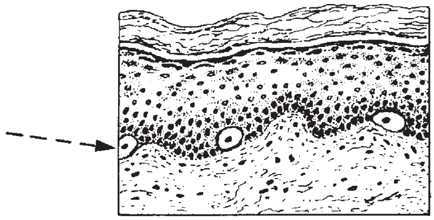


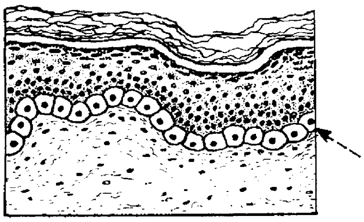
OTHER TUMOUR TYPES

BENIGN PIGMENTED NAEVUS (Melanocytic naevus or mole)

Benign pigmented naevus is extremely common. The term 'naevus' means a birthmark, but most naevi are acquired in childhood and adolescence.

During fetal life melanin-pigment-forming neuroectodermal cells migrate to the skin and are found in small numbers in the basal layer of the skin.





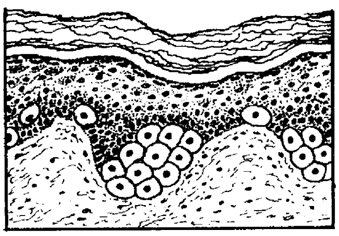
The common congenital pigmented mole is the result of an abnormality in migration, proliferation and maturation of these neuroectodermal cells. A continuous layer of pigmented cells is found adjacent to the basal epidermal cells.

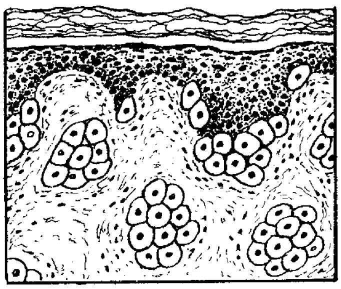
The resulting naevi vary in size and appearance, varying from small flat macular brown areas or smooth papular lesions to warty hairy excrescences. Pigmentation is variable.

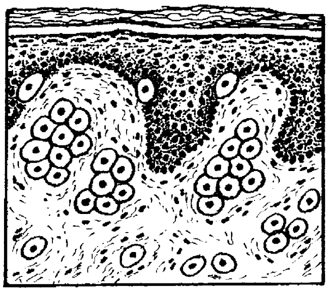
Junctional naevus
In this case proliferation is local and confined to the dermoepidermal junction.

Compound naevus
Proliferation is found in the dermis as well as the junctional area.

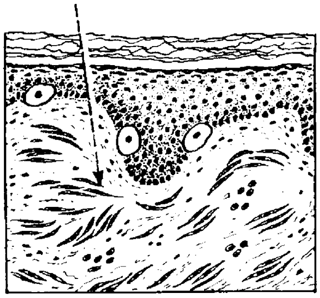
Intradermal naevus
Proliferation is wholly in the dermis.







Blue naevus is another variation in which melanocytes are arrested in migration in the dermis.



Active proliferative activity may extend into adult life, but the great majority of these lesions undergo a degree of involution. One feature which differentiates them from malignant change is that the deeper the cells penetrate the dermis the smaller they become and the less active.

OTHER TUMOUR TYPES

MALIGNANT MELANOMA

Malignant proliferation of melanocytes usually arises de novo but some melanomas arise from pre-existing naevi. Exposure to SUNLIGHT (the U.V. component) is the most important aetiological factor.

1. *Chronic* – over many years – especially relevant in the elderly.
2. *Acute* – causing burning. This is particularly important.

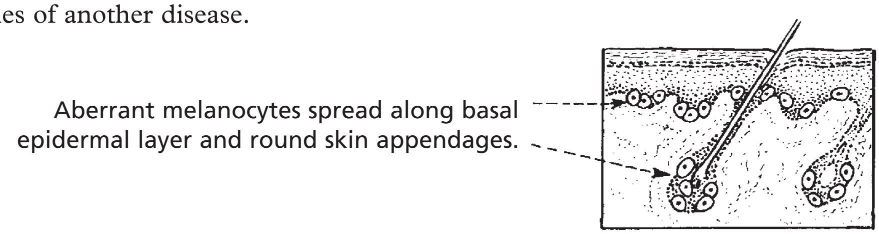
Sites

1. Skin of (a) face, soles of feet, palms of hands, nail beds,
   (b) legs (women) and (c) trunk (in men).
2. Mucous membranes of mouth, arms and genitalia – rare.
3. Eye and meninges – rare.

Some tumours are amelanotic (non-pigmented). The rate of growth is variable.

Four types of growth may occur:

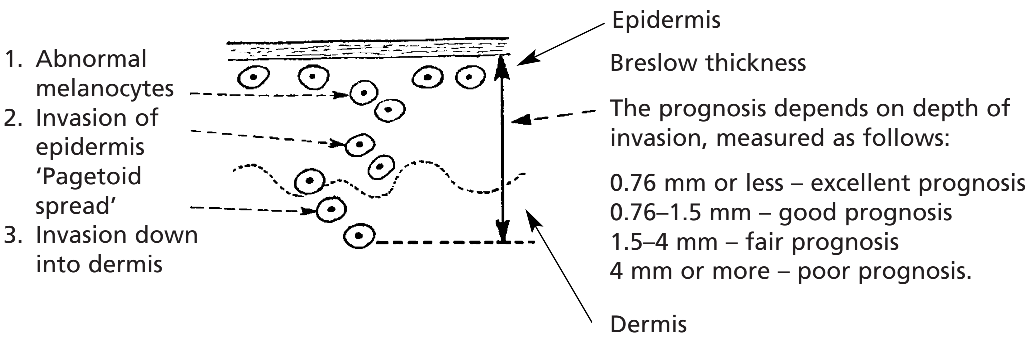
1. *Lentigo maligna* – an ‘in situ’ lesion occurring on the face of the elderly. It may spread at one edge and regress at another. It may not reach the invasive stage before the patient dies of another disease.



2. *Superficial spreading melanoma* – occurs on female leg, male trunk. It accounts for 50% of all skin melanomas in northern countries.
3. *Acral lentiginous melanoma* – found on palms of hands, soles of feet and mucous membranes.
4. *Nodular malignant melanoma* – usually on trunk. It invades early and ulceration is common.

Types 2, 3 and 4 occur in younger adults, and all can have an in situ stage.

The features of malignant melanoma are:



SPREAD OF TUMOURS

Tumours spread by several routes.

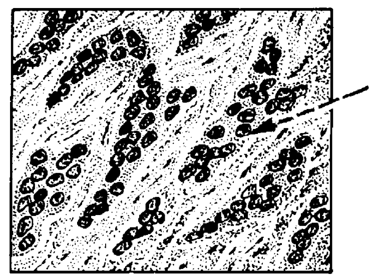
1. Local invasion.
2. Lymphatic spread.
3. Blood (Haematogenous) spread.
4. Transcoelomic spread.
5. Perineural spread.
6. Intraepithelial spread.

LOCAL SPREAD

The proliferating cells break through normal barriers.



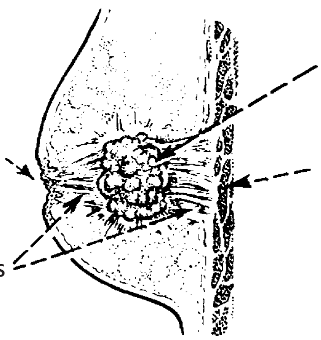
Further spread is by penetration between normal tissues.



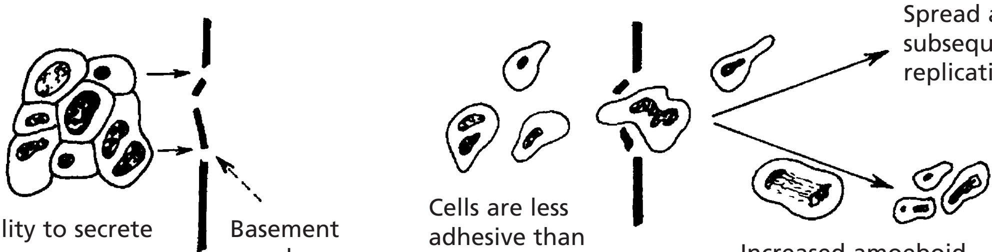
An important principle is that these permeating tumour cells take the line of least physical resistance.

Tumours may stimulate the production of new collagen fibres which are sometimes converted into dense fibrous tissue → contracts and fixes the growth to surrounding structures

e.g. Carcinoma of breast ⟶



The following diagram illustrates the basic mechanisms of cancer cell invasion.

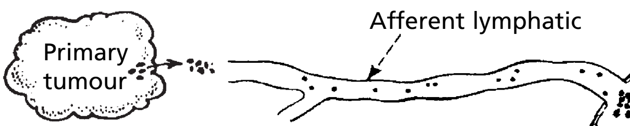


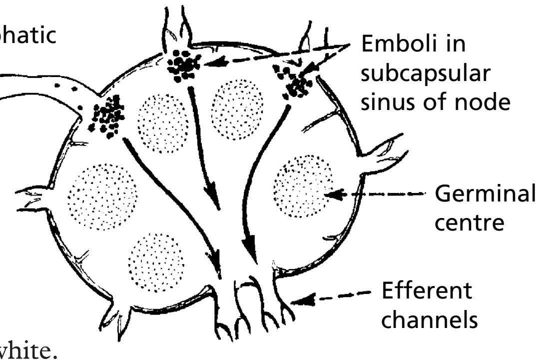
LYMPHATIC SPREAD

LYMPHATIC SPREAD

This is the commonest mode of spread of carcinomas and melanomas, but rarely of sarcomas. Malignant cells easily invade lymphatic channels from the tissue spaces.

Groups of cells form emboli in the lymph stream and are carried to the nearest node (the *sentinel node*).



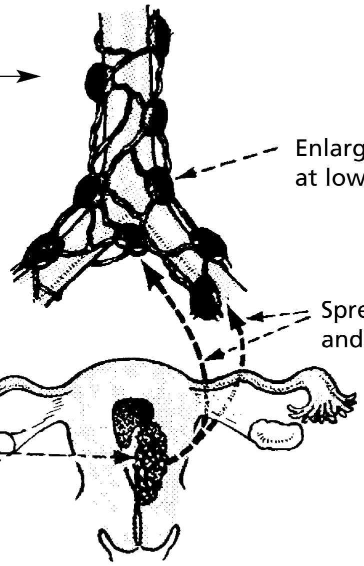


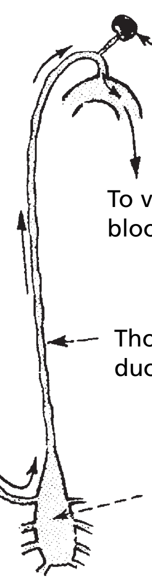
The emboli appear first in the subcapsular sinus, and then progressively invade the tissues of the node. Eventually they reach the medulla and grow into the efferent channel and produce metastases in other nodes. Invaded nodes are enlarged, firm and white.

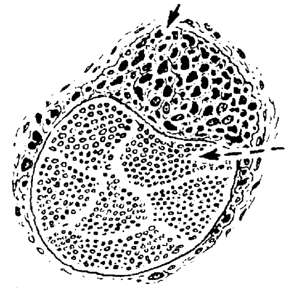
Histological examination of the sentinel node is increasingly carried out to select the patients who require extensive lymph node dissection.

LYMPHATIC SPREAD

LYMPHATIC SPREAD *(continued)*

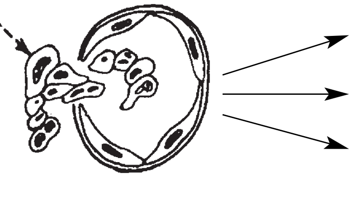






BLOOD SPREAD

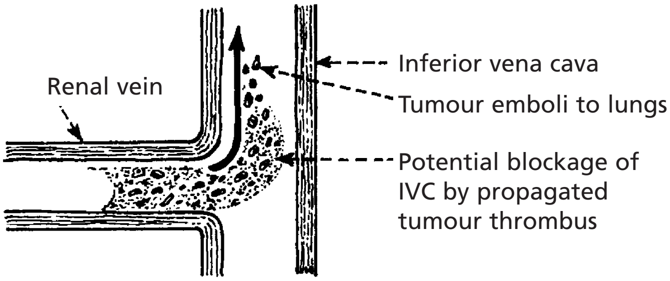
Both carcinomas and sarcomas spread by the blood stream. The entry of malignant cells into the blood is via invasion of VENULES and by lymphatic embolism through the thoracic duct into the subclavian vein.



The following are possible sequels:

1. Tumour embolism to lungs (systemic circulation).
2. Embolism to liver (portal circulation).
3. Embolism via pulmonary veins to systemic ARTERIAL circulation. (Primary and secondary lung tumours.)

VIA LARGER VEINS
Occasionally tumour thrombus is propagated from venules into larger veins. This is classically seen in RENAL CARCINOMA.



Rarely, a malignant process may be complicated by thrombosis of distant veins (thrombophlebitis migrans). This is not due to malignant invasion of the veins but is caused by the action of circulating thromboplastins formed by the tumour.

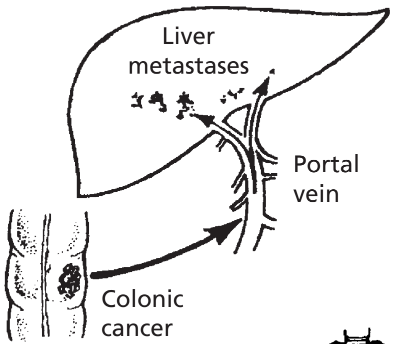
ARTERIAL SYSTEM
Direct invasion of arteries and arteriolar lumens is very rare because of the physical barrier provided by the thick muscular and elastic walls.

BLOOD SPREAD

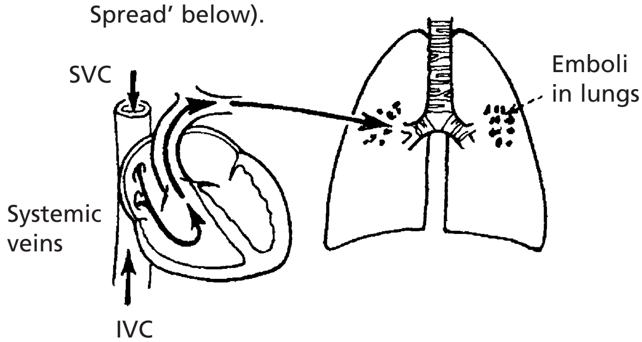
DESTINATION OF EMBOLI

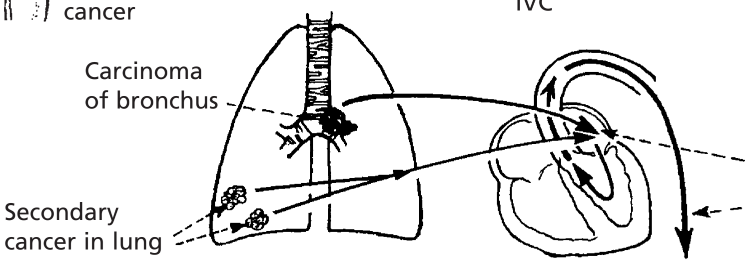
This depends on the anatomical drainage of the vessel invaded.

1. **Portal venous system** – emboli pass to liver



2. **Systemic venous system** – emboli pass to lungs. There are exceptions (see 'Retrograde Spread' below).

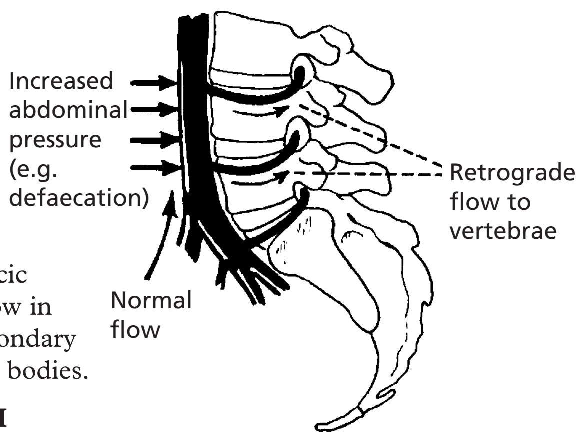




3. **Pulmonary venous system** – emboli pass to left heart and general circulation

RETROGRADE VENOUS SPREAD

As in lymphatics, growth of tumour within a vein may cause reversal of blood flow. In addition, reversal of flow is apt to happen in certain areas of the body where veins form a rich plexus and are deficient in valves, e.g. in the pelvis and around vertebrae. Changes in intra-abdominal and intrathoracic pressures easily induce changes in blood flow in these channels. It is for this reason that secondary tumours are relatively common in vertebral bodies.



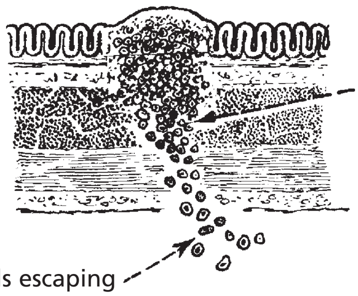
FATE of CARCINOMATOUS EMBOLI

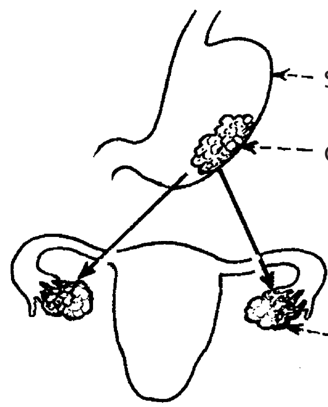
SEED and SOIL ANALOGY

The distribution of carcinomatous emboli is determined in part by anatomy, but many complex factors both in the 'seed' (the cancer cell) and the 'soil' (the potential metastatic site) are at play in the establishment of metastases at particular sites. They include surface properties of the cancer cells e.g. increased expression of **integrins** and their **receptors** present in the endothelial cells at the metastatic site. Variation in the host IMMUNE RESPONSE is also important

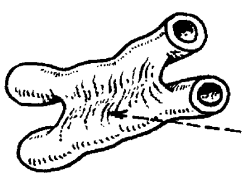
OTHER MODES OF SPREAD OF TUMOURS

TRANSCOELOMIC SPREAD (via SEROUS SACS)
This is an important and frequent route of spread in the peritoneal and pleural cavities. It also takes place in the pericardial sac.



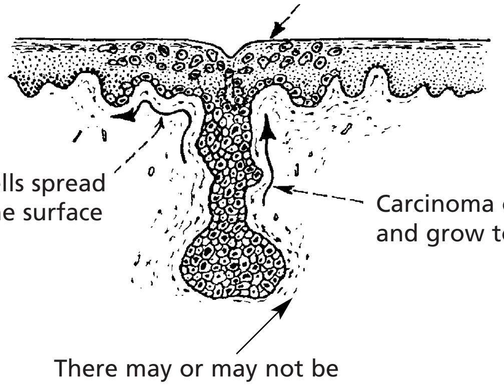


As malignant cells sink in the peritoneal cavity, they will settle in various sites. They may cause an inflammatory reaction with fibrin formation. This can cause adhesions between organs, e.g. loops of bowel.



Gastric cancer can spread to both ovaries (so-called KRUKENBERG TUMOUR). An unusual but classic manifestation.

INTRA-EPITHELIAL SPREAD
This form of spread may occur where carcinoma develops in a gland or its duct, e.g. in the breast. Carcinoma cells spread in the areolar skin. (Paget's disease of the nipple.)

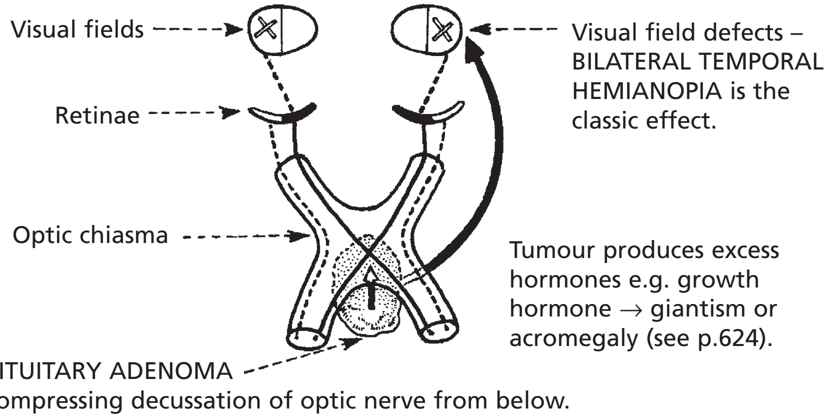


EFFECTS OF TUMOURS

BENIGN TUMOURS

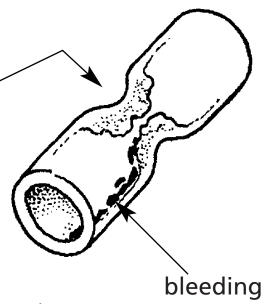
(a) The localised tumour mass may compress neighbouring structures causing loss of function and (b) benign endocrine tumours may produce excess hormones.

A Pituitary Adenoma is illustrative:



MALIGNANT TUMOURS

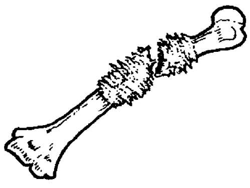
(a) **Local effects**
A tumour may narrow a hollow viscus e.g causing intestinal obstruction, ulceration and bleeding leading to anaemia.
E.g. stenosing cancer of colon



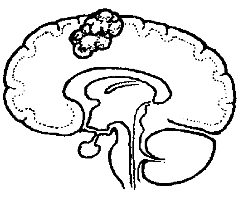
(b) **Involvement of neighbouring structures**
Direct spread compresses adjacent viscera, blood vessels and nerves – LUNG CARCINOMA is illustrative (see p.277–278).

(c) **Effects of distant metastases**
These are very numerous and variable. Two illustrative examples are given.

(i) Metastases to bone cause pain and pathological fracture.



(ii) Metastases to the brain causing epilepsy, stroke, raised intracranial pressure, etc. (see p.575).



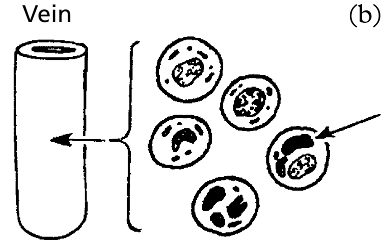
NON-METASTATIC COMPLICATIONS

Patients with cancer often have severe weight loss (cachexia), loss of appetite and fever. These are probably due to release of cytokines (e.g. TUMOUR NECROSIS FACTOR) from tumour cells. Other complications include myopathy and neuropathy. Relapsing thrombosis of distant veins (thrombo-phlebitis migrans) is due to release of thromboplastins.

TUMOUR MARKERS

Tumour cells produce substances, many of which are proteins, which are helpful in diagnosis and monitoring of treatment.

(a) Product enters blood stream (and/or urine) where it can be measured.



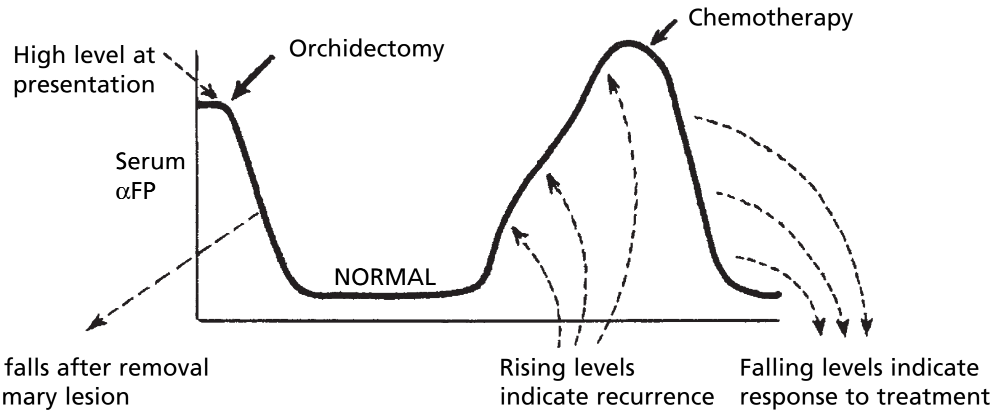
(b) Histological diagnosis is improved by identifying the specific product using immuno-staining in the cytoplasm of the tumour cells.

Some examples are:

Tumour Marker	Tumour
Human chorionic gonadotrophin (HCG)	Choriocarcinoma, Teratoma of testis
αFeto-protein (αFP)	Hepatocellular carcinoma, Teratoma of testis
Prostate specific antigen, Prostatic acid phosphatase	Prostatic carcinoma
Carcino-embryonic antigen	Gastro-intestinal and other cancers
Calcitonin	Medullary thyroid carcinoma
5-hydroxyindole-acetic acid (5HIAA) in URINE (metabolite of 5-hydroxy-tryptamine (5HT-SEROTONIN))	Intestinal carcinoid

Monitoring Treatment

Blood levels of tumour markers reflect the effects of treatment.
Example: **Testicular teratoma**



DIAGNOSIS OF TUMOURS IMMUNOCYTOCHEMISTRY

Diagnosis of tumours is made by combining clinical information with pathological information of several types:

1. *Gross Examination*
2. *Conventional Histological Assessment*
3. *Immunocytochemical staining*

Different immunocytochemical panels are used to help address specific histological dilemmas.
Thus, for a metastatic adenocarcinoma of unknown origin, the pathologist may request:

Cytokeratin profiling	CK 7, 19, 20
Transcription factors	Wilms tumour 1 (WT1) Thyroid transcription factor 1 (TTF-1) CDX2
Hormone receptors	Oestogen (ER), progesterone (PR) receptors
'Tumour markers'	Prostate specific antigen (PSA) Ca125 Carcinoembryonic antigen

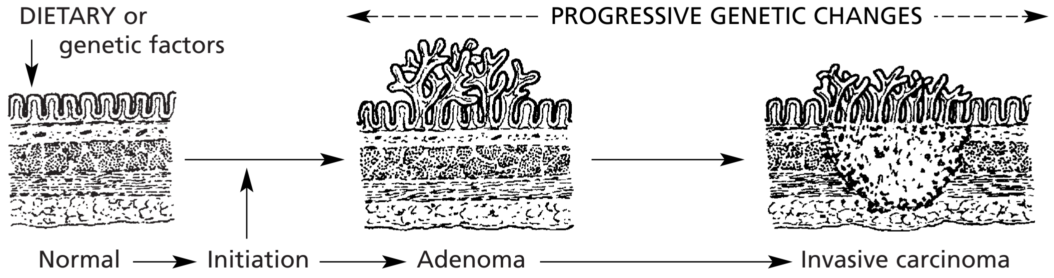
An adenocarcinoma with this profile is likely to be of pulmonary origin	CK7 +, CK20 – TTF1 +ve, WT1 –ve, CDX2 –ve ER –ve, PR –ve Ca125 –ve PSA –ve

PRE-MALIGNANCY

The pathological conditions which are associated with the development of malignancy fall into 3 groups: 1. Benign tumours, 2. Chronic inflammatory conditions and 3. Intraepithelial neoplasia.

1. **MALIGNANT TRANSFORMATION OF BENIGN TUMOURS**

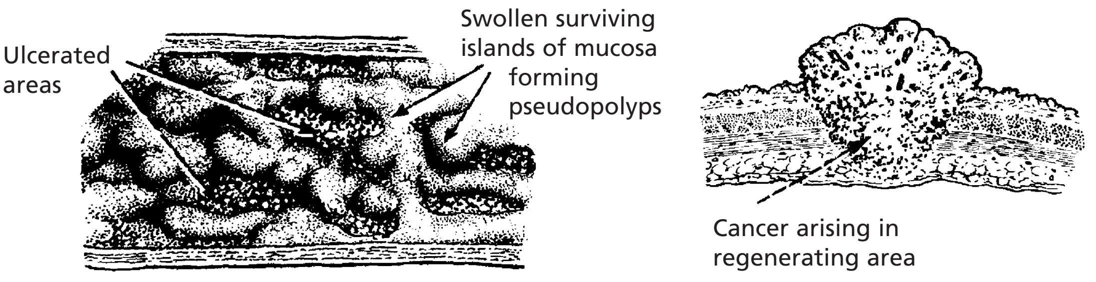
(a) **Colonic cancer** is a good example in that most arise from a benign adenoma.



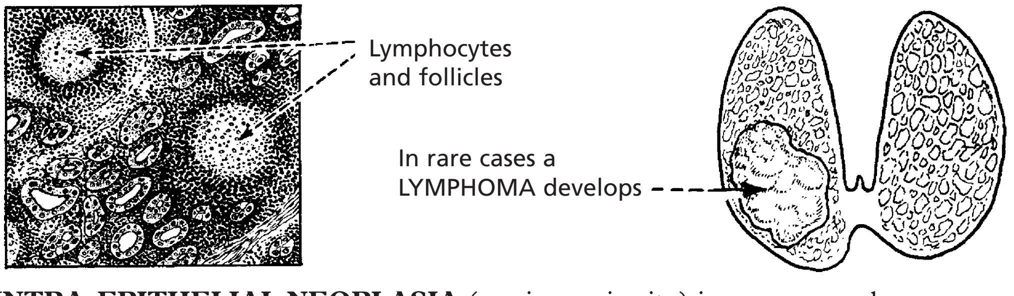
(b) In Familial adenomatous polyposis (Polyposis coli), transformation to cancer in one or more of the very numerous adenomas is inevitable (p.330).

2. **CHRONIC INFLAMMATORY CONDITIONS**
The inflammation has to be very long standing and transformation to cancer is RARE. Examples are:

(a) In **Ulcerative colitis**, repeated epithelial damage and repair increase the risk of cancer.



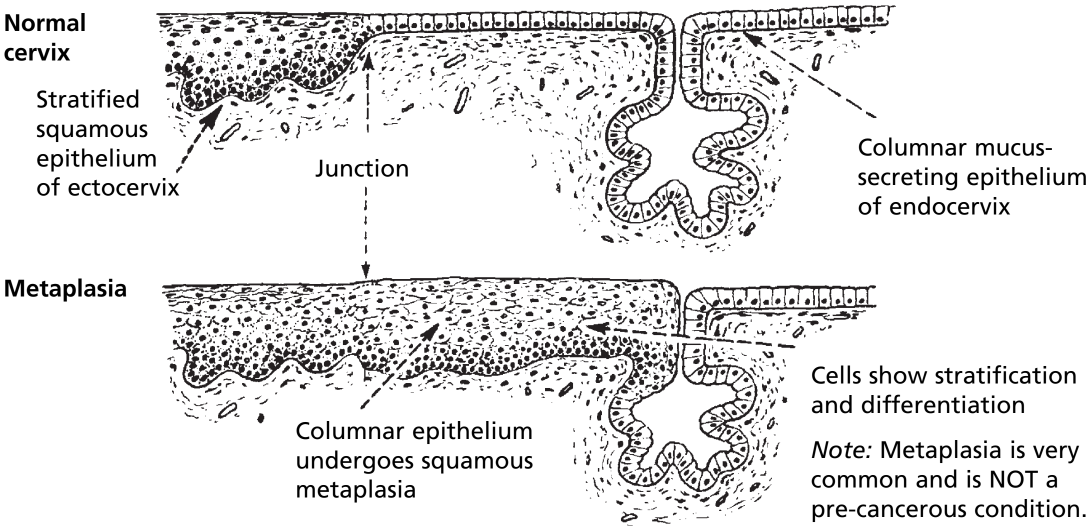
(b) In **Hashimoto's disease** – an auto-immune thyroiditis – the uniformly enlarged thyroid contains many proliferating lymphoid follicles and lymphocytes.



3. **INTRA-EPITHELIAL NEOPLASIA** (carcinoma in situ) is common and a very important pre-cancerous condition at several sites.

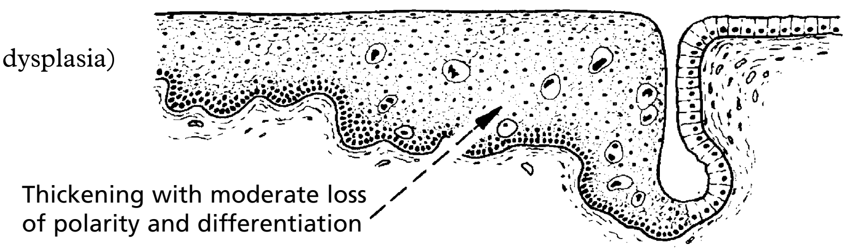
CARCINOMA IN SITU (INTRAEPITHELIAL NEOPLASIA)

This represents an intermediate stage in the production of a cancer. All the cytological features of malignancy are present, but the cells have not invaded the surrounding tissues. It is frequently found in the cervix uteri at the junction of ecto and endocervix.

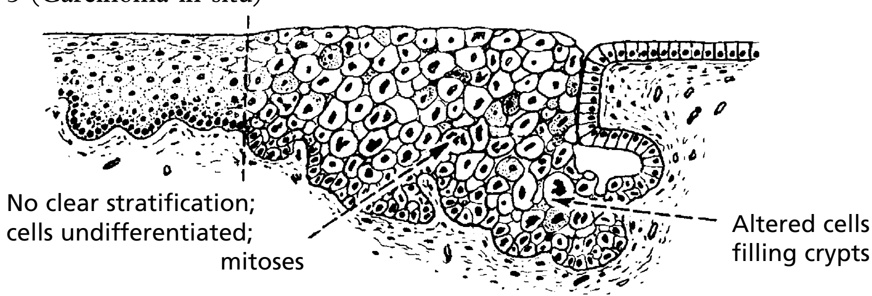


In the cervix, the abbreviation CIN (cervical intraepithelial neoplasia) is used.
There are 3 grades of severity.

1. CIN 1
   (mild dysplasia)



2. CIN 2 – appearances intermediate between Grades 1 and 3
3. CIN 3 (Carcinoma-in-situ)



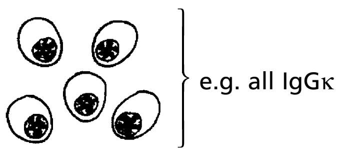
These premalignant conditions may revert to normal, but most commonly they become truly malignant and invade the surrounding tissues.
The concept of progressive premalignant proliferation applies equally in other organs (e.g. breast, stomach, oesophagus, bronchus, prostate, mouth, vulva).

CARCINOGENESIS

Malignant tumours are due to UNCONTROLLED PROLIFERATION of cells.
Most tumours are MONOCLONAL, i.e. are derived from a single transformed cell.

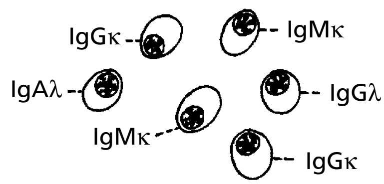
This concept is well illustrated in MULTIPLE MYELOMA – a malignant tumour of plasma cells.

All the tumour cells produce the same immunoglobulin – including the same light chain.



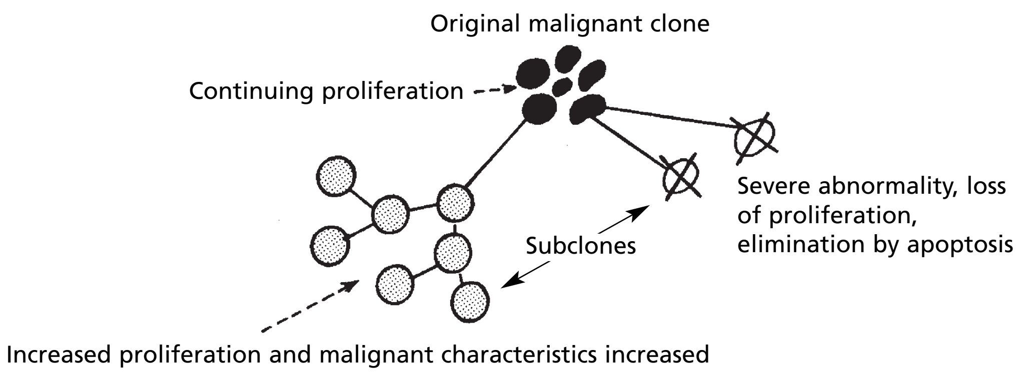
See also page 96.

In contrast, an inflammatory infiltrate of plasma cells is POLYCLONAL…



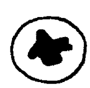
… producing various immunoglobulins and light chains.

CLONAL EVOLUTION
In time, some cells undergo further mutations which are passed on to their progeny. This is called clonal evolution or progression and explains the morphological variations seen in tumours. Some of the subclones grow more rapidly and metastasise more readily while others are so abnormal that proliferation is not possible and the clone dies out.



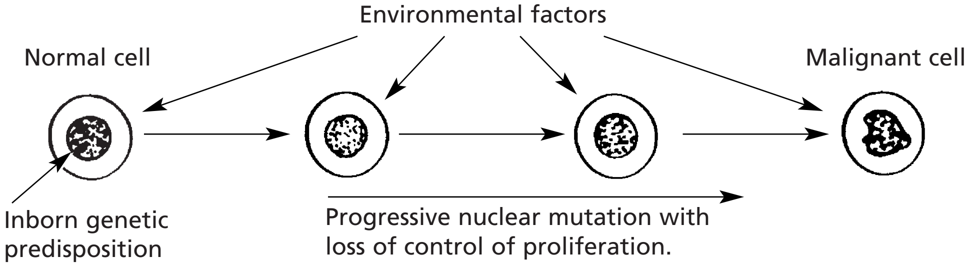
Nuclear morphology and DNA content
In histological sections these abnormalities are indicated by variations in nuclear density (usually increased), size and shape (i.e. PLEOMORPHISM).

The term 'POLYPLOIDY' is used when the nuclear DNA is increased by exact multiples of the normal.

'ANEUPLOIDY' indicates irregular increases in DNA content.→ 

CARCINOGENESIS

A number of factors, both environmental and genetic, contribute to a cell undergoing malignant change. This should be regarded as a multistep sequence (see p.154).



ENVIRONMENTAL FACTORS

The 3 major environmental factors which induce tumours are 1. Chemical carcinogens, 2. Radiation and 3. Viruses.

CHEMICAL CARCINOGENESIS

Historically, chemical agents were the first to be associated with cancer. Now, many are recognised in (a) industrial processes, (b) social habits and (c) diet.

Industry	Tumour	Chemical Responsible
Aniline dyes	Bladder cancer	Naphthylamine
Insulation e.g. shipbuilding, building	Mesothelioma, lung, laryngeal cancer	Asbestos
Mineral oil and tar	Skin cancers	Benzpyrene and other hydrocarbons
Plastics	Angiosarcomas of liver	Vinyl chloride monomer
Wood dust	Cancer of nose and sinuses	?

Social Habits

Cigarette smoking is strongly associated with the development of many cancers, including lung, mouth, larynx and bladder. Chewing tobacco greatly increases the risk of oral cancer. It is likely that air pollution, e.g. combustion products of petrol and diesel, also contributes to carcinogenesis. Obesity is associated with an increased risk of cancer, e.g. of the uterus and colon.

Diet

Chemicals in food may be carcinogenic. Nitrosamines may be formed by the action of bacteria on ingested nitrites. AFLATOXINS are produced by fungi (*Aspergillus flavus*) and, by contaminating foodstuffs, may cause liver cancer.

Note: Chemical carcinogens may act in 2 ways:
1. Directly at the site of application or portal of entry, e.g. skin and lung cancers.
2. After modification, either at the sites of metabolism or excretion e.g. liver and urinary tract tumours.

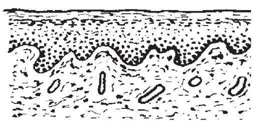
CARCINOGENESIS

CHEMICAL CARCINOGENESIS *(continued)*

This is a multistep process of long duration.

The stages of **initiation** and **promotion** are important and were identified in classic experiments of skin carcinogenesis.

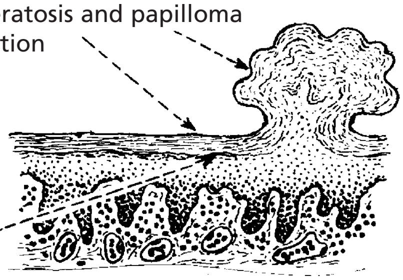
1. **Normal skin**



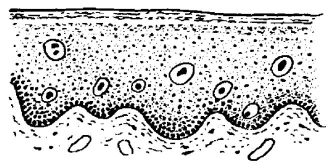
Application of carcinogen, e.g. Benzpyrene (a mutagen).

2. **INITIATION** Skin appears normal but important changes have occurred in the cell's DNA.

3. **PROMOTION** – initiated by co-carcinogens e.g. croton oil, turpentine. (These agents are not mutagenic but act by stimulating cell proliferation.) Visible surface and histological changes are seen.

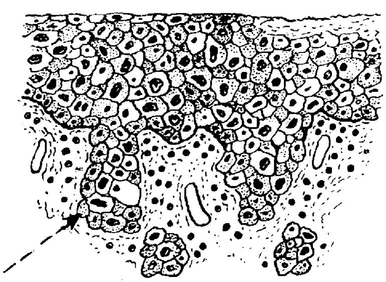


(b) Dysplasia, i.e. cytological features of malignancy, but no invasion (see p.144).



These stages are reversible.

4. **Appearance of MALIGNANT TUMOUR** (An irreversible change)



The order of application of these agents is important. No tumour follows application of promotor alone, or promotor followed by initiator.

In rodents, these changes take months; in humans the time scale is years and is exemplified in the skin, cervix uteri, bronchus, urinary bladder, colon and breast.

CARCINOGENESIS

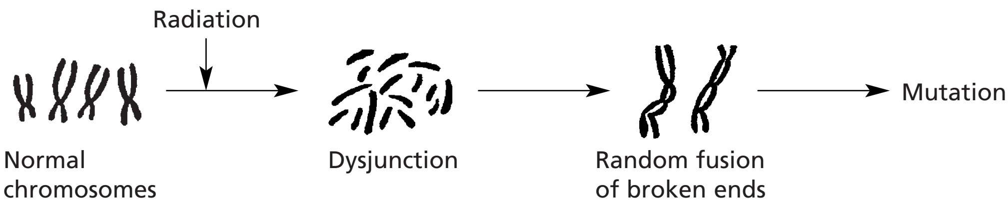
RADIANT ENERGY

The potential dangers from irradiation give much cause for concern.

Source of Radiation	Tumours	Type of Radiation
Sunlight	Melanoma, Carcinoma of skin	Ultraviolet (non-ionising)
Nuclear explosions (e.g. atom bombs, Chernobyl)	Leukaemia, carcinomas of lung, breast, thyroid	Ionising
Therapeutic irradiation	Various carcinomas, sarcomas, leukaemia	Ionising
Mining radioactive substances (e.g. uranium)	Lung carcinomas	Ionising
X-ray workers (historical)	Skin cancer, leukaemia	X-rays: Ionising

Effects of Irradiation on Cells

The ionising effect of radiation damages the cell's DNA, especially during cell proliferation, ranging from single gene mutation to major chromosome damage, including breaks, deletions and translocations.



Proliferating cells are particularly vulnerable. Marrow and gastro-intestinal mucosa are highly sensitive.

Ultraviolet light is of low energy and mainly affects the skin. The 'PYRIMIDINE DIMERS' formed by UV light are normally excised by DNA repair mechanisms. In **xeroderma pigmentosum**, these are deficient leading to numerous skin tumours.

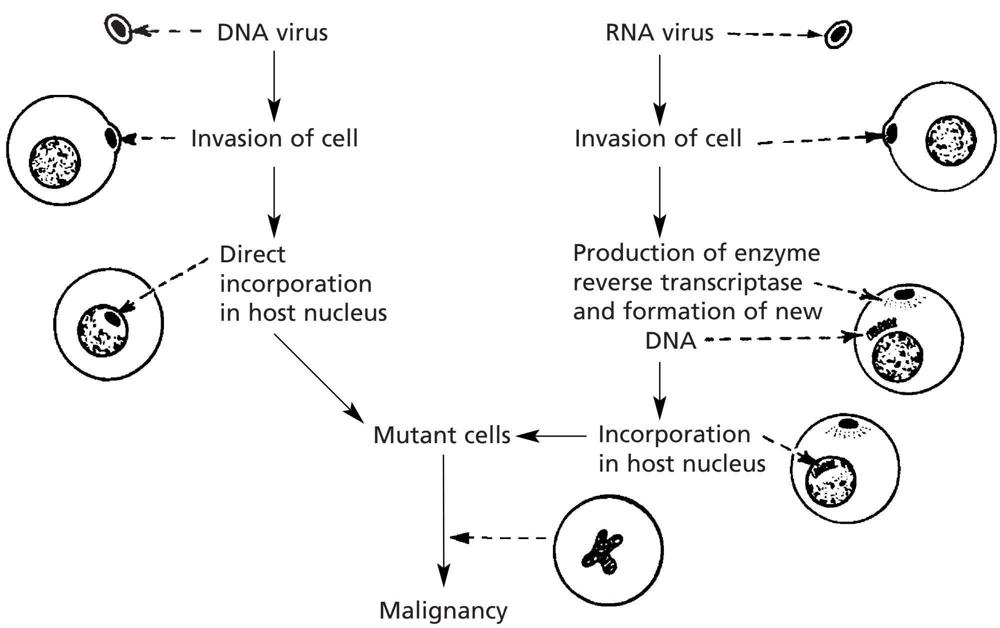
CARCINOGENESIS – VIRUSES

Viruses have long been known to cause cancer in animals (e.g. Rous sarcoma virus and the mouse mammary tumour virus – the Bittner milk factor).

In recent years viruses have been shown to contribute to the development of some human cancers.

Virus	Type	Tumour type
Epstein-Barr (EBV)	DNA	Burkitt's lymphoma, nasopharyngeal cancer, Hodgkin's disease, post-transplantation lymphoma
Human herpes virus 8 (HHV-8)	DNA	Kaposi's sarcoma
Hepatitis 'B'	DNA	Hepatocellular carcinomas
Human papilloma virus (HPV)	DNA	Cervical, penile, anal carcinoma
Human 'T' cell leukaemia virus (HTLV-1)	RNA (Retrovirus)	T-lymphoblastic leukaemia

Mode of action of oncogenic viruses
The essential feature is addition of new DNA to the nucleus of host cells resulting in mutants, but the way in which this is achieved differs in the two types of virus.

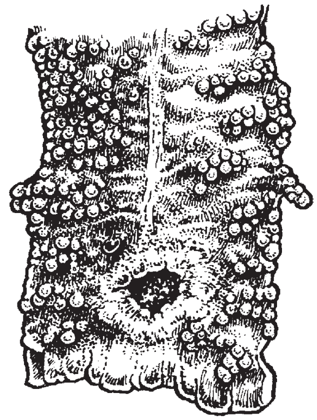


CARCINOGENESIS – HEREDITY

The inherited genetic influences in cancer are now well recognised.

1. There is a high risk of cancer in some uncommon syndromes inherited as Mendelian traits. Illustrative examples are:

   (a) **Familial adenomatous polyposis coli** (APC). An autosomal dominant condition. Numerous polyps occur in the colon in late childhood (10–14 years) and inevitably lead to adenocarcinoma in early middle age (30–45 years). The APC gene responsible lies on chromosome 5.



   (b) **Xeroderma pigmentosum.** An autosomal recessive trait where failure of DNA repair mechanism leads to skin cancer.

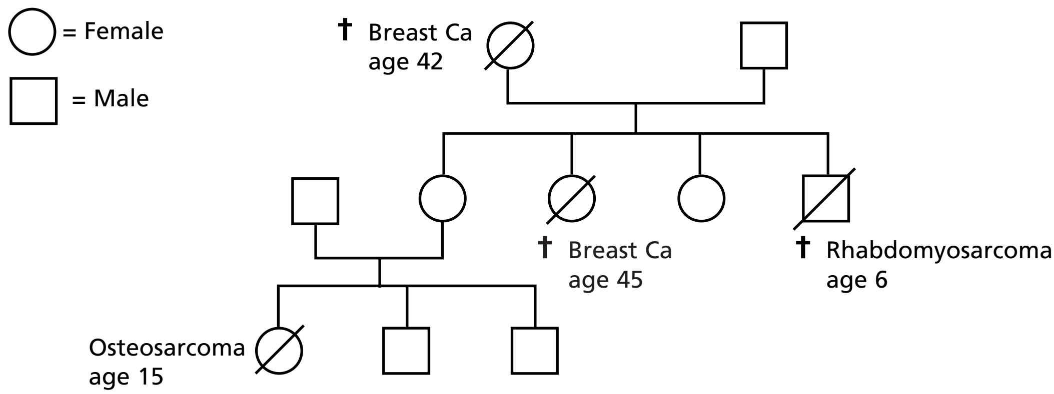
   (c) **Neurofibromatosis** – multiple neurofibromas (NF) – with a 1% risk of sarcoma, is due to a defect of NF-1 gene on chromosome 17.

   (d) **Retinoblastoma** – an autosomal dominant condition (Rb gene on chromosome 13), (p.153).

2. A less well defined, but strong familial tendency, is seen with some common tumours. For some the gene is identified, e.g. BRCA-1 gene, chromosome 17, – 60% risk of breast or ovarian cancer by 50 years.

3. In some families, there is a high risk of several types of cancer. In the rare Li-Fraumeni syndrome, childhood sarcomas, breast cancer in young women, and many other cancers are seen. This is due to a germ-line mutation of the p53 gene (p.153).

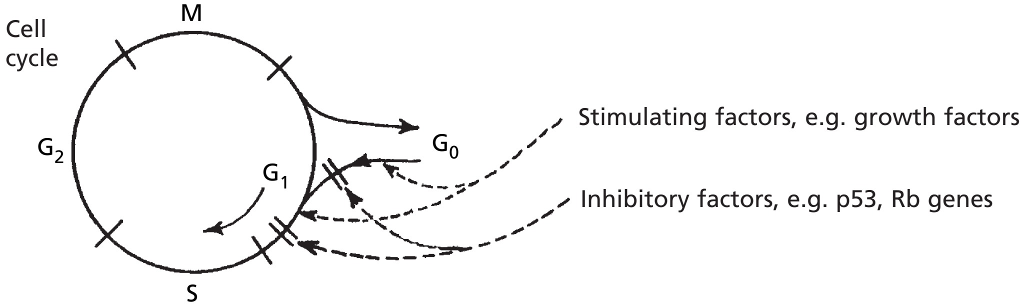
Illustrative Family Tree:



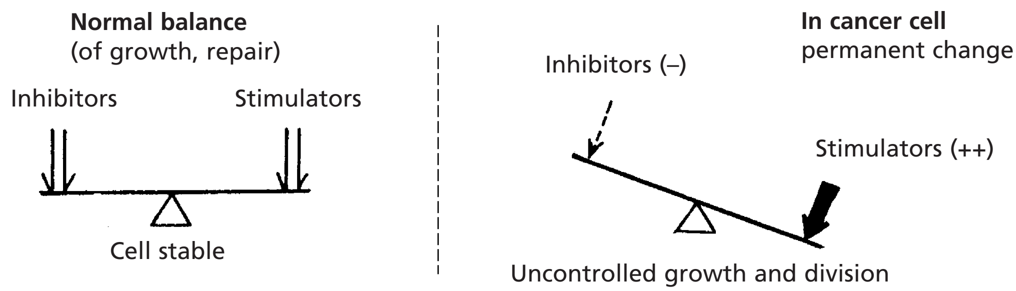
/ = denotes affected.

ONCOGENES AND TUMOUR SUPPRESSOR GENES

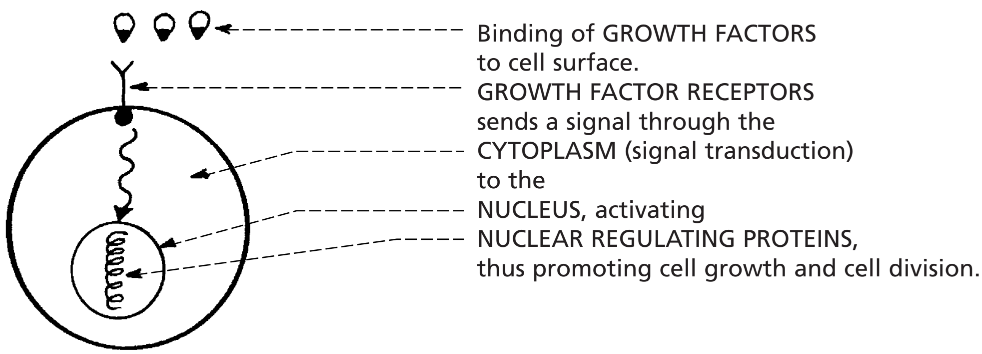
Cellular proto-oncogenes are NORMAL genes which STIMULATE cell division. Tumour suppressor genes are NORMAL genes which INHIBIT cell division. Their normal activity during somatic growth and in regeneration and repair takes place during the G_0–G_1 phase of the cell cycle and is strictly controlled.



In cancer cells the normal controls are defective so that the balance between factors stimulating and inhibiting cell growth is permanently lost, resulting in increased proliferation.



Cellular proto-oncogenes code for a number of proteins involved in cell proliferation:



In the cancer cell, these normal genes are permanently changed to ONCOGENES and proliferation is uncontrolled.

Mutation or overexpression of genes which normally control APOPTOSIS (p.4) are increasingly recognised in many tumours, e.g. overexpression of *bcl-2* inhibits apoptosis in follicular lymphoma (p.432).

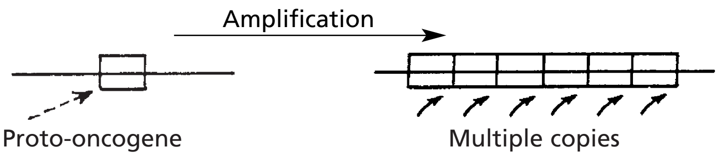
ONCOGENES

The production and activity of ONCOGENES is complex and there are many ways in which they are activated.

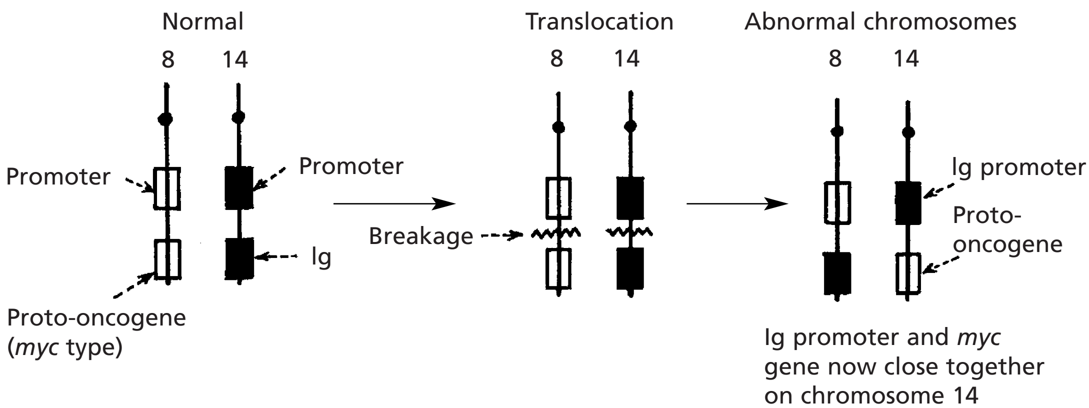
The following are examples.

1. **Production of excess NORMAL protein**

   (a) Gene amplification, e.g. neuroblastoma (*myc* type gene)

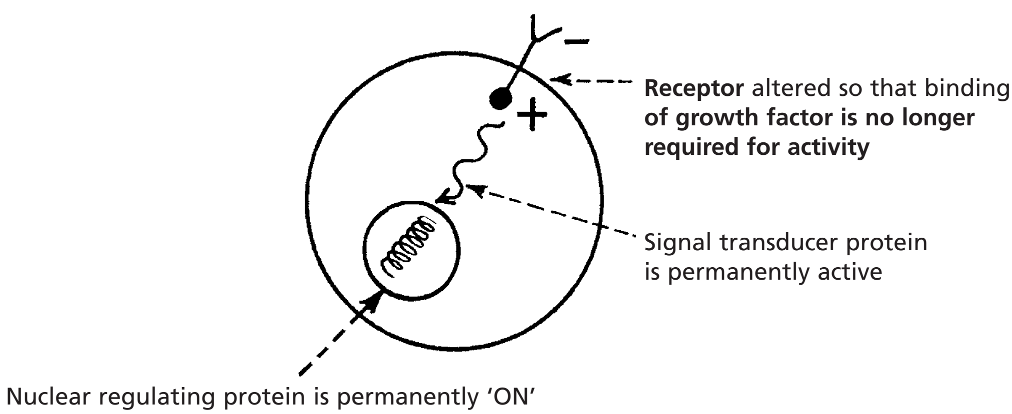


   (b) Increased mRNA transcription due to chromosomal translocation, e.g. in Burkitt's LYMPHOMA chromosomes 8 and 14 are involved.



   The *myc* oncogene is now under the influence of the Ig gene control and is permanently switched on.

2. **Production of FUNCTIONALLY ABNORMAL PROTEIN**
   A point mutation of the proto-oncogene produces a protein with an altered function so that over-stimulation occurs.
   Altered **growth factor receptor function** is an example.



TUMOUR SUPPRESSOR GENES

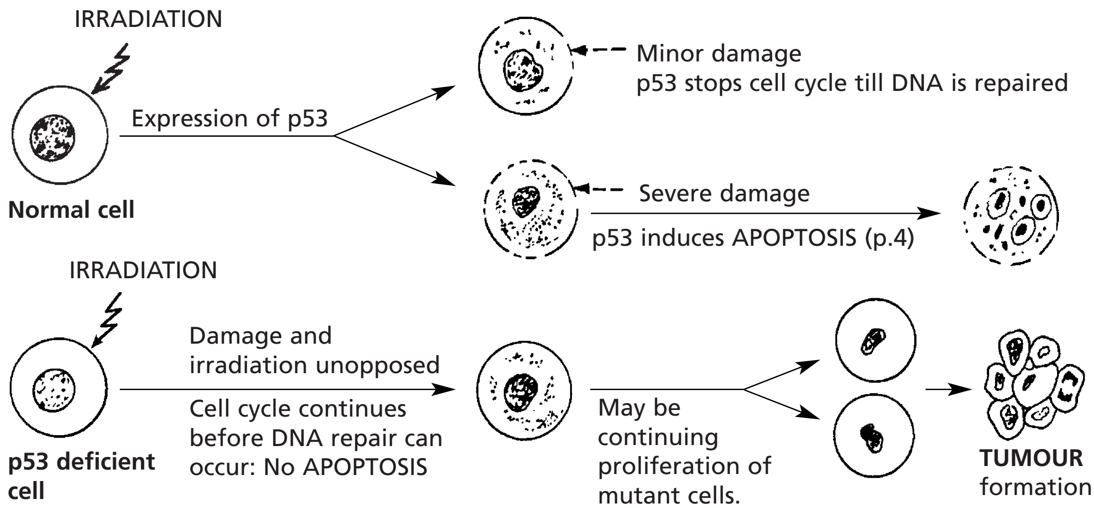
Tumour suppressor genes are normal genes which switch off cell proliferation by acting on the cell cycle in G_1. Their biological role is much broader than simply suppressing tumour function, but the name reflects how they have been discovered.

Loss of *both* copies of a tumour suppressor gene is required for cancer to develop. In contrast, only one copy of a given oncogene needs to be activated to cause excess proliferation.

Examples are:

Tumour suppressor gene	Chromosome	Tumours
p53	17	Carcinoma of lung and breast: sarcoma
Retinoblastoma (Rb)	13	Retinoblastoma, sarcoma: some carcinomas
NF1	17	Neurofibromas, malignant peripheral nerve tumours
APC	5	Colonic carcinoma
WT1	11	Wilms' tumour, bladder cancer, breast cancer, rhabdomyosarcoma

p53 gene: This gene codes for a nuclear phosphoprotein, which is expressed in increased amounts following cellular damage, e.g. **irradiation**.

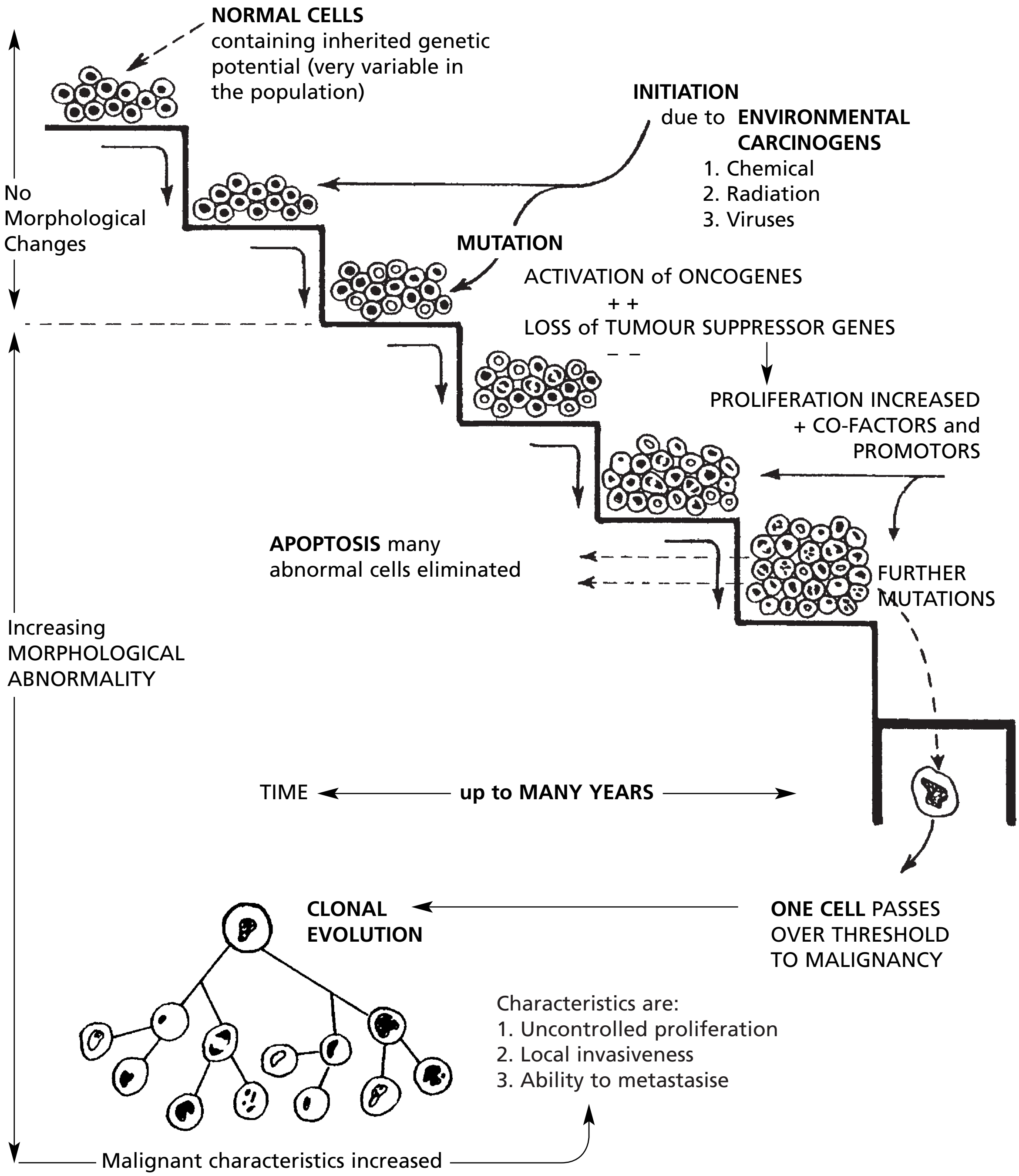


p53 has been called the 'Guardian of the genome'. Abnormalities of p53 are found in at least 30% of all cancers.

Germ line p53 mutation is a feature of the Li-Fraumeni syndrome.

CARCINOGENESIS – SUMMARY

The MULTISTEP STAIRWAY to MALIGNANCY



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CHAPTER 7

CARDIOVASCULAR DISEASES

GENERAL CONSIDERATIONS

Cardiovascular diseases are the commonest cause of death in Westernised communities. The main forms are:

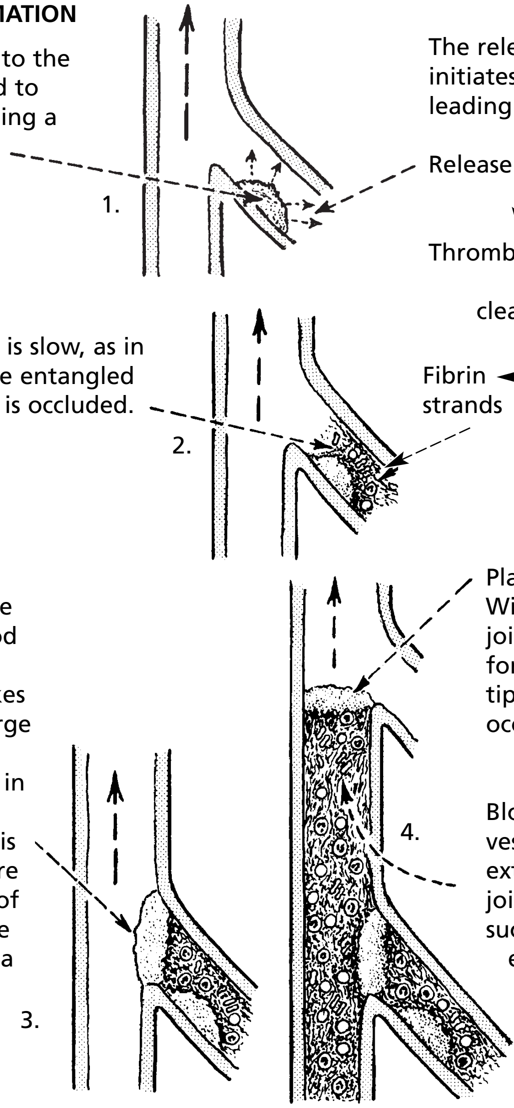
1. **Ischaemic heart disease** and 2. **Cerebrovascular diseases.**

The following general abnormalities of circulation are common to both.

THROMBOSIS

A thrombus is a mass formed from blood constituents within a vessel or the heart during life. Blood clotting is a physiological protective mechanism but thrombosis is a pathological process with serious consequences.

MECHANISM OF FORMATION



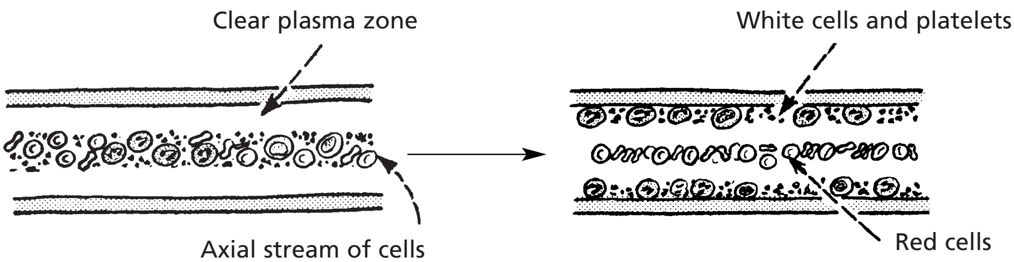
FACTORS LEADING TO THROMBOSIS

The 3 MAIN factors leading to thrombosis are known as Virchow's triad:

1. Alterations of blood flow.
2. Damage to endothelium of vessel.
3. Changes in composition of the blood.

1. ALTERATIONS OF BLOOD FLOW

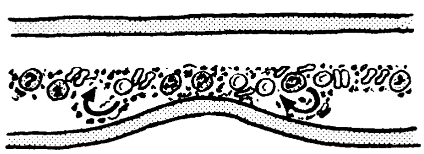
The main effect is to bring platelets into contact with the vessel wall. This results from: **Slowing of blood flow**, e.g. in cardiac failure or during bed rest. With slowing, the normal axial stream of blood cells is lost and white cells and platelets fall out of the main stream and accumulate in the peripheral plasma zone.



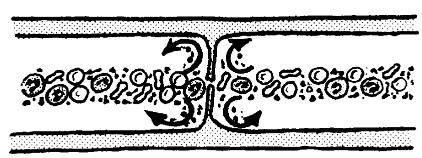
Turbulence, e.g. by deformation of vessel wall or around venous valves.

Local increase in lumen, as in varicose veins or aneurysm, causes eddies and platelets and white cells fall out of main stream.





Swelling or compression of vessel wall by disease. Eddies form in front and behind obstruction.



Eddies form around valves if flow slows.

These changes in flow and shear stress cause altered endothelial function with increased production of agents which promote thrombosis (p.160).

FACTORS LEADING TO THROMBOSIS

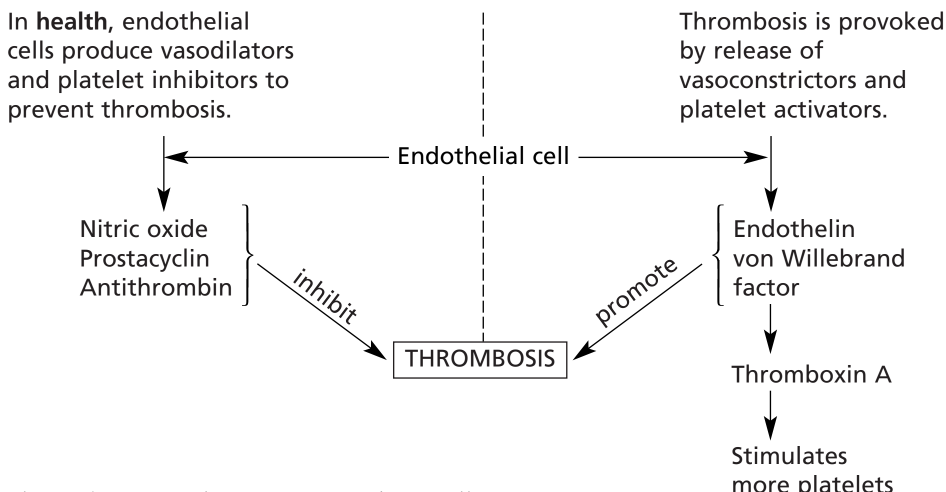
2. **DAMAGE TO ENDOTHELIUM OF VESSEL**

This leads to platelet adhesion and aggregation. Common causes are:

(a) Disease in vessel wall, e.g. atheroma.



(b) Toxins from nearby inflammatory processes.
(c) Local compression of vessels (e.g. during operations).



The balance between these processes is usually AGAINST THROMBOSIS.

3. **CHANGES IN COMPOSITION of the BLOOD**

(a) INCREASE in platelets, fibrinogen and prothrombin after operations and childbirth: usually after 5–10 days.
(b) INCREASE in platelet adhesiveness – again after surgery.
(c) Rare inherited abnormalities of thrombosis inhibitors – e.g. antithrombin III deficiency, protein C deficiency.
(d) Miscellaneous factors – e.g. oral contraceptives, smoking, some cancers.

COMMON SITES AND TYPES OF THROMBUS

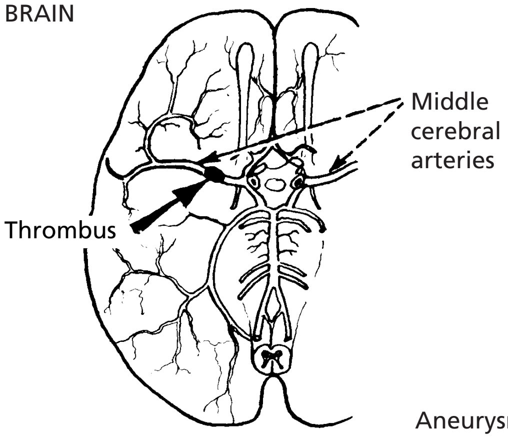
ARTERIAL

Thrombi are common in arteries as a complication of **atheroma**. Forming in a rapid circulation, the thrombus consists mainly of PLATELETS (WHITE thrombus).

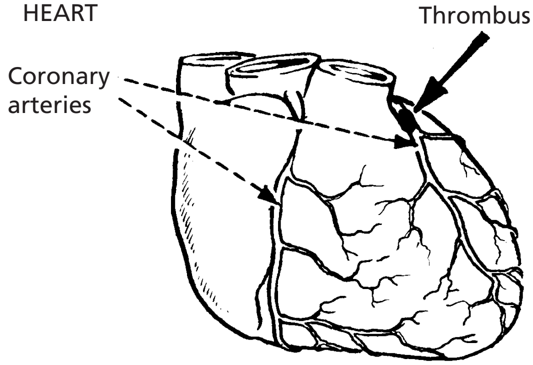


Common sites include:

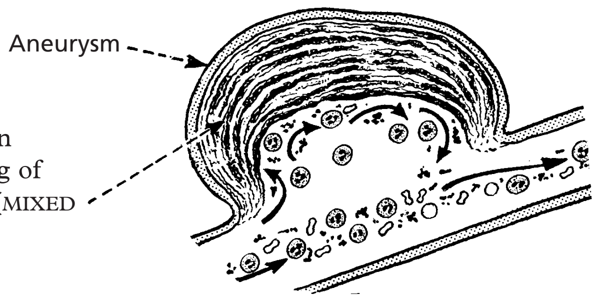
BRAIN



HEART

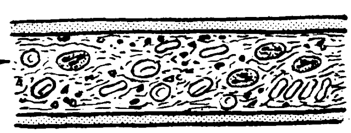


Thrombus formation is common in the walls of **aneurysms**, consisting of layers of red and white thrombus (MIXED or LAMINATED thrombus).

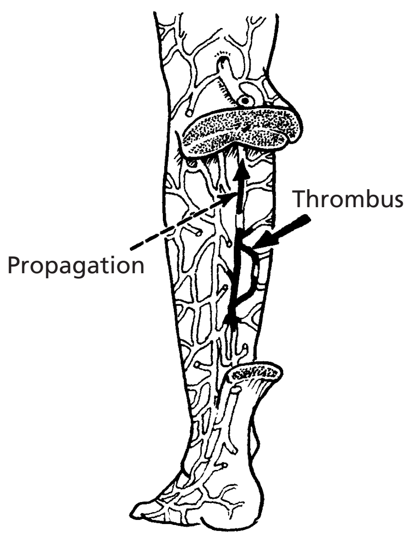


VENOUS

Systemic venous thrombosis is common because of the slow blood flow and lower pressure. It consists of red cells, platelets and fibrin (RED thrombus).



It is most common in the deep veins of the calf and frequently propagates in the femoral and iliac veins – from where it may embolise to the lungs (p.164).



Bed rest, operations and cardiac disease are predisposing conditions.

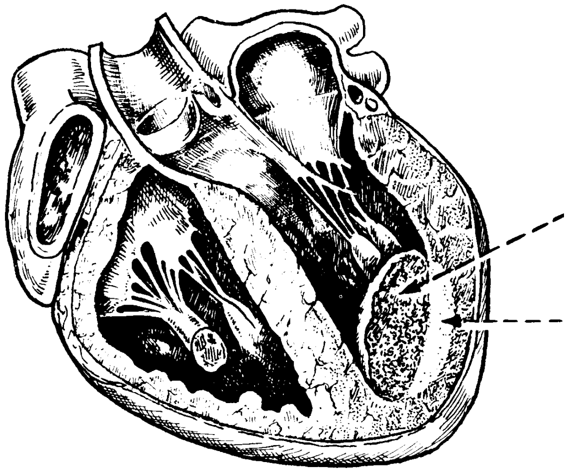
Portal thrombosis is a rare complication of abdominal disease, e.g. hepatic cirrhosis.

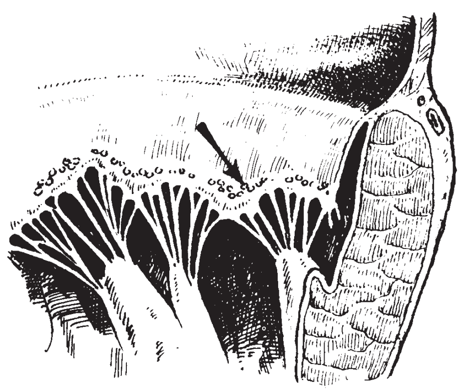
COMMON SITES AND TYPES OF THROMBUS

CAPILLARY
Thrombi, composed mainly of fused red cells, form when capillaries are damaged, usually in acute inflammatory processes.

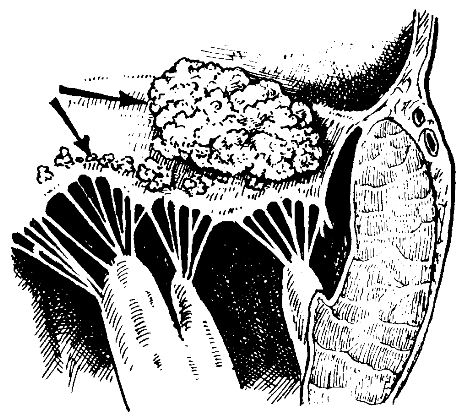
Capillaries are occluded by fibrin thrombi in cases of disseminated intravascular coagulation (DIC – see p.414).

CARDIAC
Thrombi may be seen in the ATRIA (especially in the auricles in ATRIAL FIBRILLATION); in the VENTRICLES and on the heart VALVES.





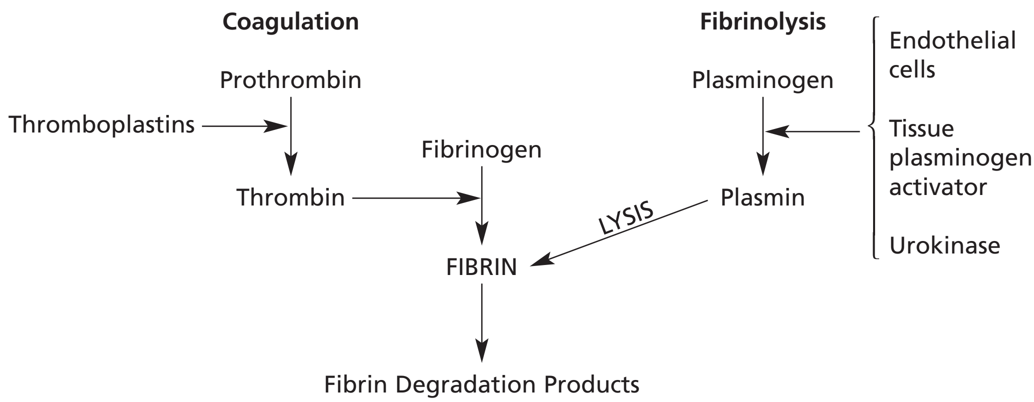
Thrombi can occur on the heart valves in rheumatic endocarditis.



In infective endocarditis thrombi form on the valves. They are larger, mixed, friable and contain masses of micro-organisms.

SEQUELS OF THROMBOSIS

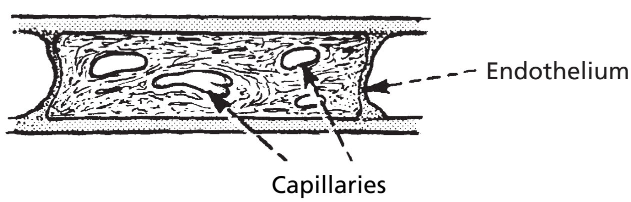
1. **FIBRINOLYSIS**
   Many small thrombi are completely removed by the Fibrinolytic System which exists to limit thrombosis.



2. **EMBOLISM**
   Part of the thrombus may be detached and carried along in the blood stream to impact in a distant vessel. This is extremely important clinically.

3. **ORGANISATION**
   Capillaries grow into the point of thrombus attachment within a day or two. Fibroblasts and phagocytic cells accompany the capillaries, and gradually the thrombus material is dissolved and replaced by fibrovascular tissue. At the same time endothelium covers the ends of the thrombus, thus limiting the thrombotic process.

   Ultimately, the branching capillaries may be converted into one or two larger vessels which may restore the circulation through the vessel – RECANALISATION.



4. **CALCIFICATION**
   In diseased vessels, organisation may not take place. The thrombus shrinks, calcium salts are deposited and convert it into a phlebolith – seen in X-rays.

5. **INCORPORATION**
   A mural thrombus, e.g. in a large artery, may be covered by endothelium and incorporated in the vessel wall. This process may be important in the formation of atheroma.

PROPHYLAXIS and THERAPY of thrombosis aims at:

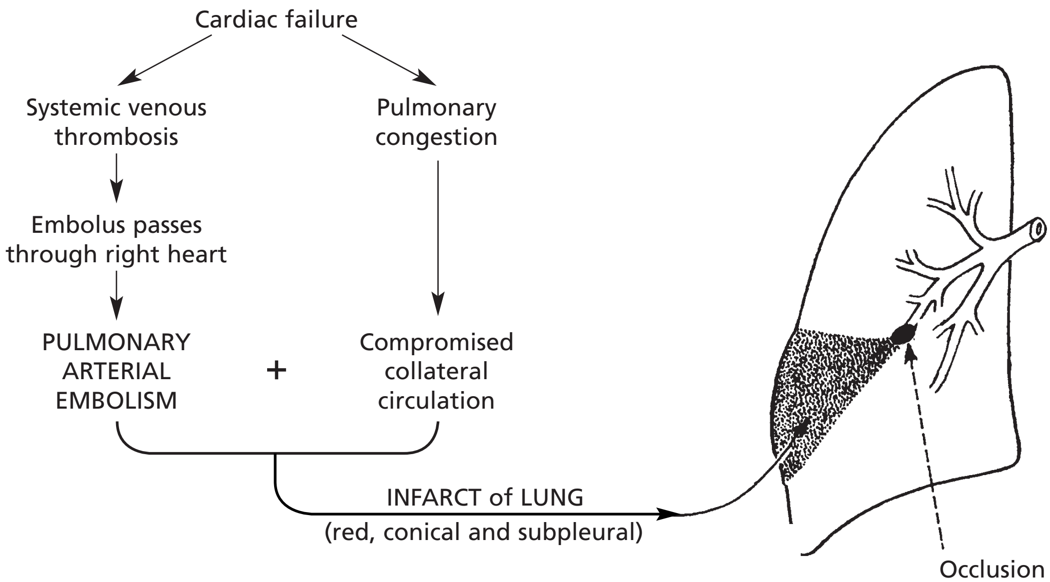
1. Reducing coagulability utilising (a) anticoagulants aimed at specific sites in the coagulation cascade, e.g. warfarin derivatives, heparin (see p.413) and (b) inhibiting specific prostaglandin synthesis, e.g. aspirin.
2. Encouraging fibrinolysis, using fibrinolysins.

EMBOLISM

An embolus is any abnormal mass of matter carried in the blood stream and large enough to **occlude some vessel**.

The commonest emboli are derived from material generated within the vascular system, e.g. fragments of thrombus or material from atheromatous plaques.

1. **Pulmonary thrombo-embolism**
   Emboli from the systemic veins (especially deep venous thrombosis, e.g. in the calf) pass through the right side of the heart to the pulmonary circulation. The consequences depend on the size of the embolus and the patient's previous health.
   (a) **Massive** embolus → blocks main pulmonary artery trunk → acute total circulatory block → SUDDEN DEATH.
   (b) **Moderate** embolus
   As the lungs have a double blood supply (pulmonary and bronchial arteries), and a vast anastomosis, obstruction of a pulmonary artery branch does not necessarily cause infarction. If, however, there is pre-existing cardiac failure, infarction may occur as the bronchial arterial blood flow is sluggish.



   (c) **Small** emboli
   Many are removed by the fibrinolytic system and are asymptomatic. However, repeated minor emboli may result in pulmonary hypertension and right heart failure.
   Repeated small emboli → blockage of peripheral pulmonary arterial branches → **pulmonary hypertension**.

2. **Emboli of the arterial system** are derived from the heart or the larger arteries which have become atheromatous. The results of arterial obstruction are very important.

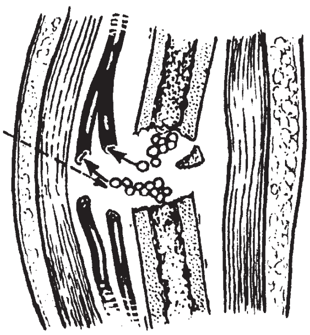
EMBOLISM

EMBOLISM – Other forms

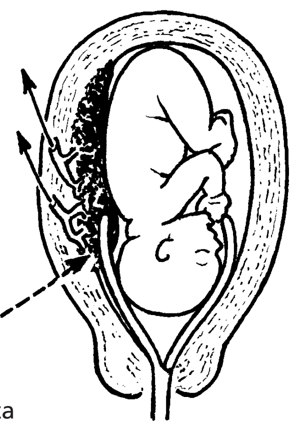
Matter entering the vascular system may be:

(a) *Solid* – tumour cells, bacterial clumps, fat, parasites.
(b) *Gaseous* – air.
(c) *Liquid* – amniotic fluid with fetal derived matter.

Fat embolism
This may occur when a long bone is fractured, usually 24–72 hours later. Fat globules enter torn veins and pass to the lungs; obstruction of pulmonary blood flow may be sufficient to cause *anoxia*. Cerebral symptoms are common due to anoxia but also due to the fat globules which have passed through the lung capillaries.



Amniotic fluid embolism
During childbirth, amniotic fluid may enter a uterine vein, especially after manipulations. Vernix, hairs and squames enter the circulation. In addition to embolic phenomena, there are also coagulation disorders (p.413).



Embolism in drug addicts
Foreign material (e.g. talc) may enter the bloodstream following intravenous injection and form emboli.

Air embolism

(a) *Single embolism*
Atmospheric air may enter the blood when a neck or intracranial vein is incised. Inspiration induces a suction effect by causing a negative pressure in the veins. As a result of frothing in the right ventricle, cardiac function is seriously impaired.

(b) *Multiple embolism*, in ‘caisson disease’
This occurs in people working in barometric pressures of several atmospheres, e.g. diving to great depths. The atmospheric gases go into solution in high concentration in the blood and tissues. If decompression occurs too quickly, these gases ‘boil’ off and appear as bubbles in the circulation. The oxygen is taken up by the tissues but insoluble gases cause widespread ‘embolism’, especially in the nervous system and bone.

ARTERIAL OBSTRUCTION

Arterial obstruction is usually due to thrombosis or embolism and may be (i) partial or complete, (ii) acute or slowly progressive.

The effects depend on the local anatomy, particularly on the presence of an anastomotic collateral circulation.

Occlusion of end arteries

These may have (a) no collaterals (e.g. splenic artery),
(b) capillary anastomoses (e.g. renal and coronary arteries),
(c) arterial anastomoses which are too small to maintain circulation (e.g. superior mesenteric artery).

Result:

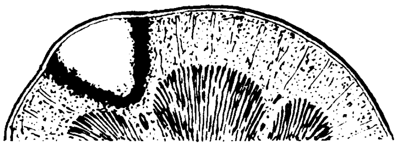
Obstruction → anoxia of tissues → necrosis

INFARCTS

An infarct is an area of necrosis due to ischaemia. It is often found at the periphery of an organ, e.g. the kidney.



After 12 hours: Area is pale. Degenerative changes already seen with electron microscope.



After 36 hours: Area shows pallor and swelling due to coagulative necrosis. The surrounding tissues are congested.

Healing

This takes place slowly. Capillaries and fibroblasts replace the necrotic tissue. Collagen is formed, the fibroblasts contract and this results in a depressed scar.

IMPORTANT SITES OF INFARCTION

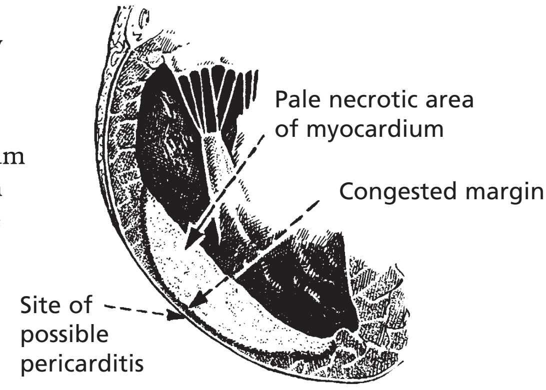
The HEART, the LUNGS and the BRAIN are the most common sites. Less common are the SMALL INTESTINES and the kidney and spleen.

IMPORTANT SITES OF INFARCTION

HEART (p.175)
Infarction is almost always due to coronary arterial thrombosis complicating atheroma.

Cardiac function is immediately compromised, eddies form, the endocardium may be damaged and a thrombus forms on the inner surface of the infarcted area. The damage may extend to the external surface causing pericarditis.

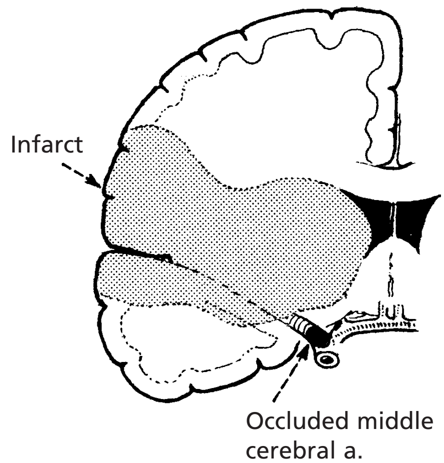
If the patient survives, the infarct heals by fibrosis.



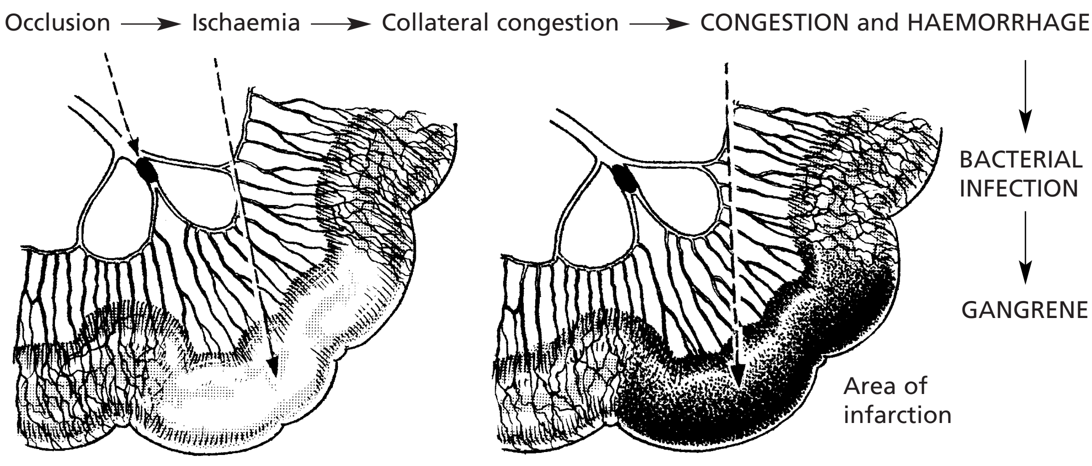
BRAIN (p.177)
Infarcts are commonly due to thrombosis of diseased vessels or to embolism from the left heart or carotid arteries, e.g. MIDDLE CEREBRAL, posterior cerebral and basilar arteries.

The usual changes of infarction take place, but the necrosis is colliquative – **cerebral softening.**

Infarction may occur without arterial occlusion in severe, prolonged hypotension (shock). Parts of the brain at the junction of arterial territories are affected (boundary zone or watershed infarcts) (see p.177).



INTESTINE
Infarction may follow thrombosis of or embolisation to the mesenteric arteries. The sequence of changes usually seen in solid organs is altered by the effects of anastomoses and, in the later stages, by **bacterial invasion** (gangrenous necrosis).

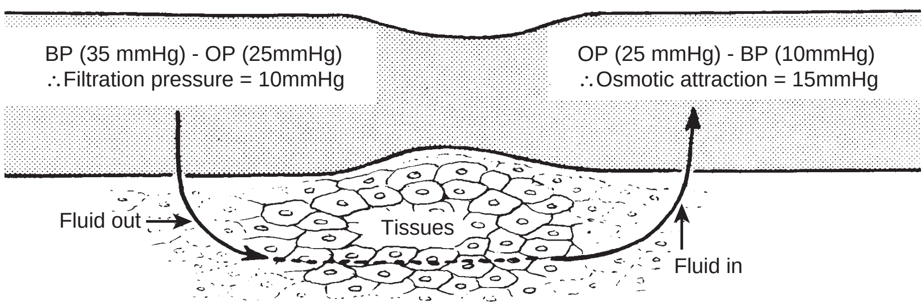


NORMAL TISSUE FLUID CIRCULATION

There is continuous interchange of fluid between blood and tissues. Some fluid enters the lymphatics before eventually returning to the blood stream. Two main forces operate pressure gradients controlling the fluid movement.

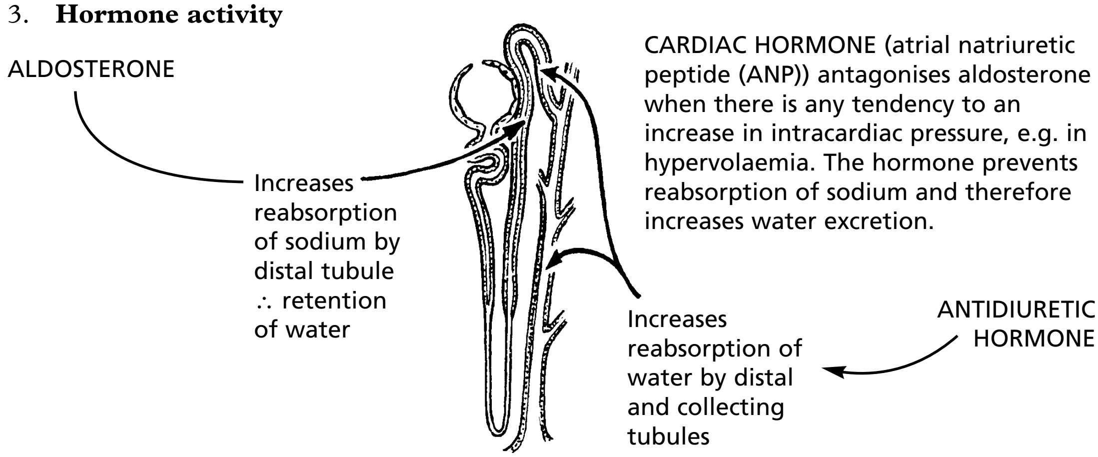
1. ***Hydrostatic pressure***, i.e. capillary blood pressure (BP) encouraging the passage of fluid through the capillary wall, = 35 mm mercury.
2. ***Protein osmotic pressure*** (OP), i.e. the plasma proteins encourage the retention of fluid in the capillaries to maintain osmotic equilibrium. This pressure is equivalent to 25 mm mercury.

At the arterial end the blood pressure is greater than the osmotic pressure and fluid is forced out of the capillary. The reverse is true at the venous end and fluid is attracted into the vessel.



A small amount of fluid enters lymphatics. This is partly the result of tissue pressure and partly due to osmotic attraction of proteins in the lymphatic system.
In addition to those forces operating at capillary level, there are other mechanisms which influence the movement of fluid within the body.

1. **Fluid intake**
   Intake via the gut or parenterally may exceed the ability of the kidneys to eliminate water.
2. **Integrity of the kidneys**
   Damage to the kidney may diminish the elimination of fluid.
3. **Hormone activity**



OEDEMA

Oedema is an accumulation of excess fluid in the extravascular tissues. It can be local or generalised. There are a wide variety of causes.

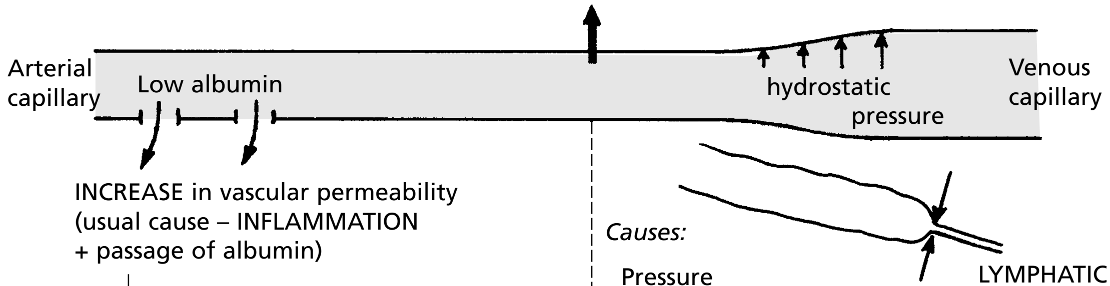
DECREASE in blood osmotic pressure
(usually due to HYPOALBUMINAEMIA)

Common causes:
- Liver disease – deficient synthesis.
- **Renal disease** – protein loss.
- Starvation.

INCREASE in venous pressure
(hydrostatic pressure ↑)

Common causes:
- **Cardiac failure**
- Venous obstruction in lower limbs.

NET INCREASE
in FLOW from CAPILLARY



INCREASE in vascular permeability
(usual cause – INFLAMMATION
+ passage of albumin)

↓

Loss of osmotic pressure

Causes:

Pressure by tumour

Parasites

LYMPHATIC OBSTRUCTION prevents local lymph flow

More than one factor may apply:

E.g. **Cirrhosis** of liver (p.349)

↓	↓
Hypoalbuminaemia	Portal venous hypertension
↓	↓
Low osmotic pressure	Raised hydrostatic pressure

↘ ↙

ASCITES
(Fluid accumulates in the peritoneal cavity)

Cerebral (p.532) and pulmonary (p.187) oedema are life threatening and are dealt with separately.

SHOCK

Shock is a condition in which there is reduced perfusion of the vital organs due to a severe and acute reduction in cardiac output and effective circulating blood volume. There is progressive cardiovascular collapse characterised by hypotension, hyperventilation and clouding of consciousness.

CAUSES

1. **HYPOVOLAEMIC (i.e. diminished blood volume)**
   Associated with:

   (a) **Trauma**
   - (i) Severe haemorrhage – external or internal
   - (ii) Severe injury – especially fractures of bones and crushing of tissues
   - (iii) Burns – especially where extensive surface damage allows loss of a large amount of exudate.

   (b) **Dehydration** – in cases of severe vomiting, diarrhoea or diabetic ketoacidosis.

2. **CARDIOGENIC**
   Acute diseases of the heart – especially myocardial infarction – in which there is a sudden fall in cardiac output.

3. **SEPTIC** (bacteraemic, endotoxic)
   In serious bacterial infections (especially Gram-negative organisms, e.g. *E. coli*).

4. **ANAPHYLAXIS** – a severe immune hypersensitivity reaction (p.101).

EFFECTS

The loss of effective circulating blood causes tissue and cell damage. At the same time, there are reactive changes in the circulation.

These two mechanisms combine to cause the shock syndrome.

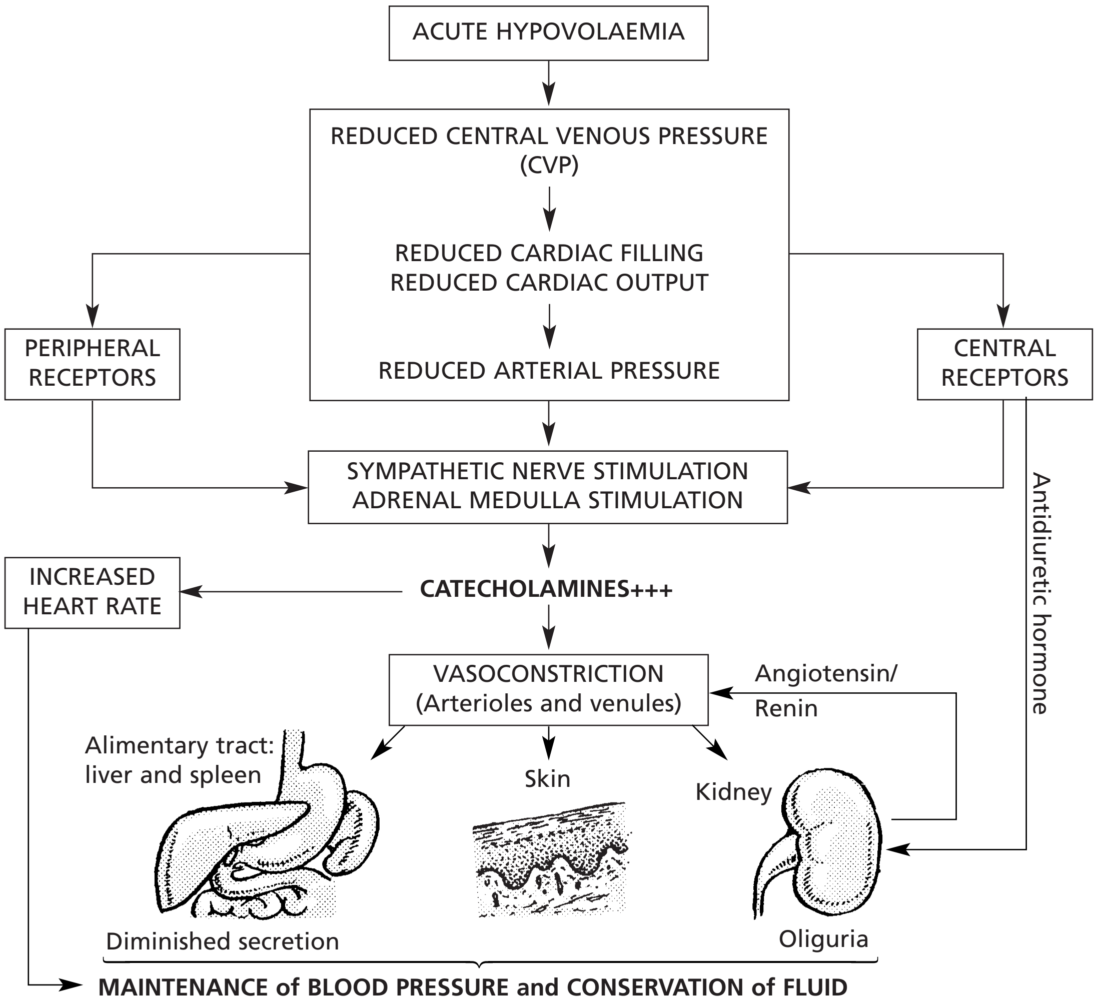
The main consequences of shock are:

1. Low cardiac output.
2. Hypotension.
3. Impaired tissue perfusion.
4. Cellular hypoxia.

SHOCK

REACTIVE CIRCULATORY CHANGES – EARLY STAGE

These changes are concerned with the maintenance of an adequate cerebral and coronary circulation and are effected by redistribution of the blood in the body as a whole.



Note: Salt and water are retained due to aldosterone from the adrenal cortex.

At the same time, the circulations in the brain and heart are protected by autoregulatory mechanisms. They are not subject to the generalised vasoconstriction.

Instead:

DILATATION of → CEREBRAL and CORONARY → ARTERIES → maintains satisfactory flow down to blood pressures of 50–60 mmHg

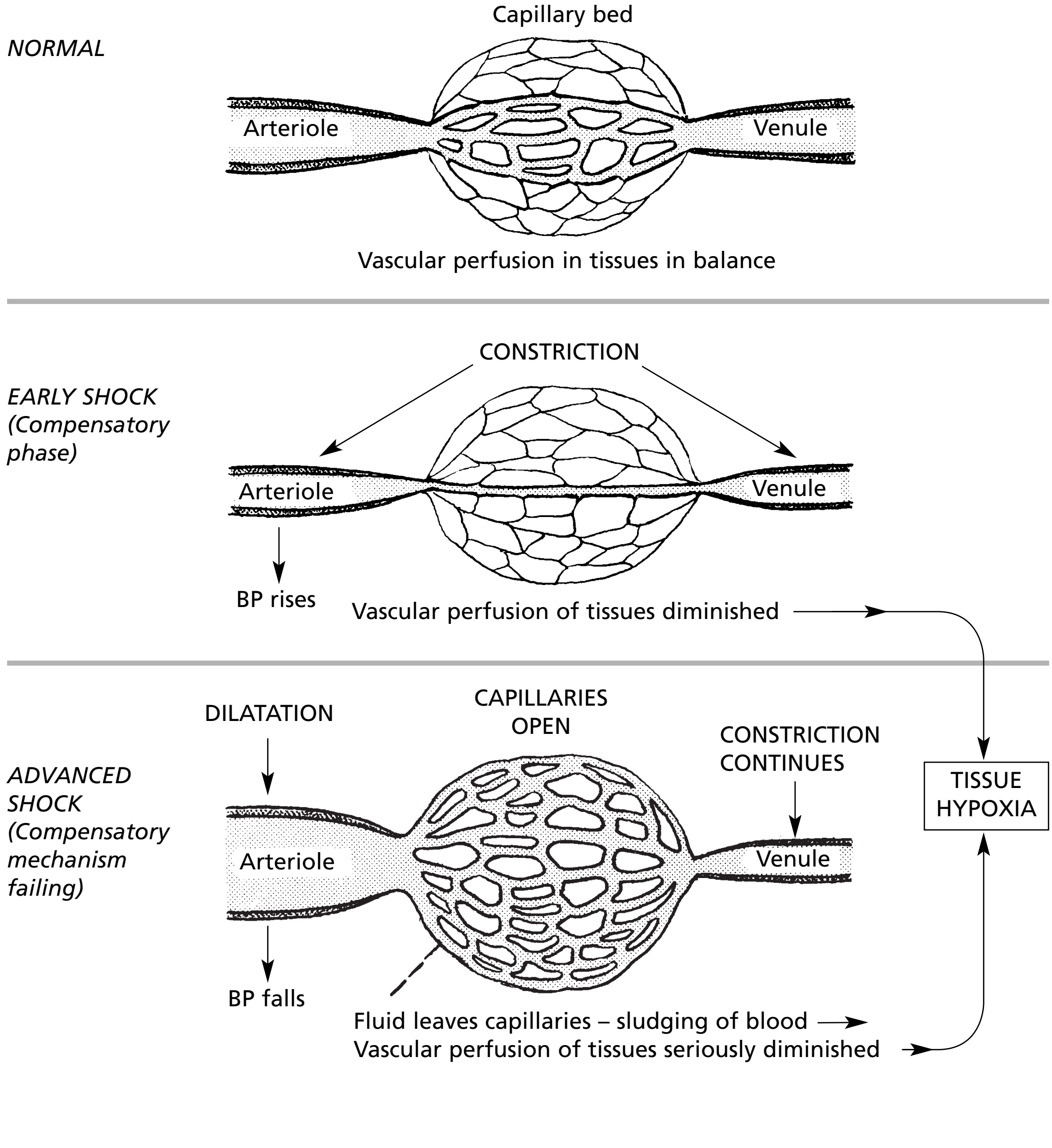
If the loss of circulating fluid volume is great, the limits of the compensatory mechanism are exceeded and the patient develops severe shock.

SHOCK

DECOMPENSATION – ADVANCED STAGE

The patient is now listless, pale and cold, the face is pinched and the lips blue. The pulse is rapid and weak and the blood pressure is low.

Conditions in Vascular bed

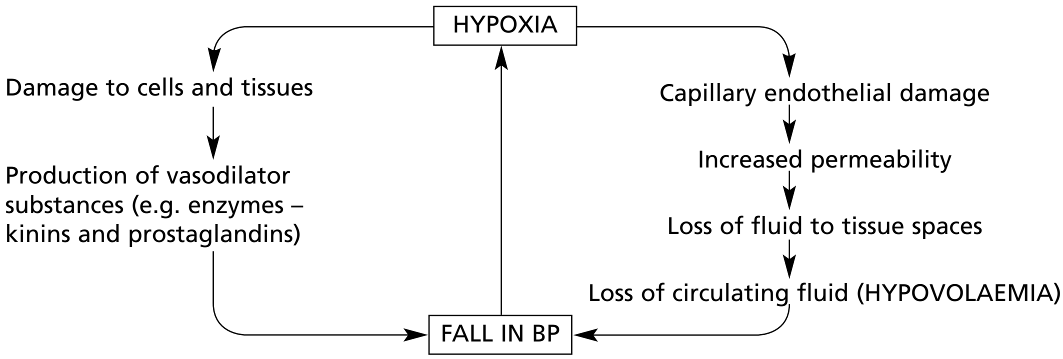


SHOCK

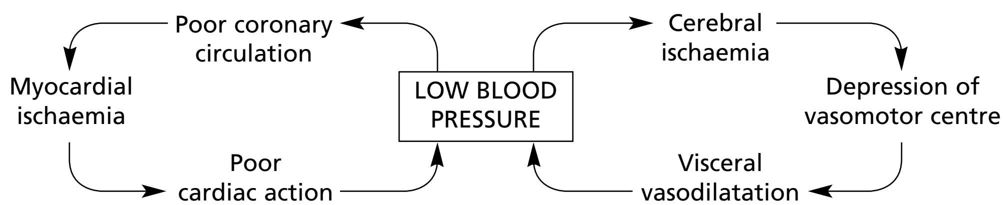
DECOMPENSATION – ADVANCED STAGE *(continued)*

Thus, from the beginning of the shock process, all the body tissues, with the exception of the brain and the heart, suffer from hypoxia. This sets up vicious circles which aggravate the condition:

1.



2. When the blood pressure falls below 50–60 mmHg, the autoregulatory control of the cerebral and coronary circulation fails. Serious damage to the brain and heart may occur.



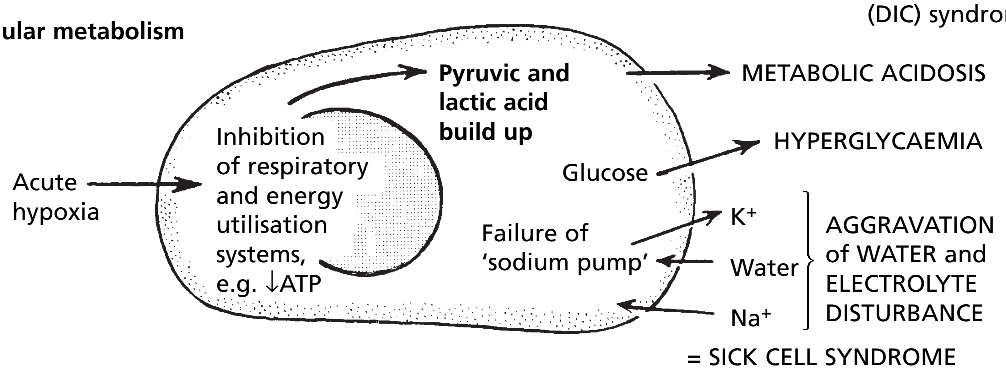
CHANGES IN THE BLOOD AND CELL METABOLISM

As well as these basic circulatory disturbances, important changes in the blood and cellular metabolism occur in shock.

Blood coagulation system

Acute hypoxia → Damaged endothelium → Coagulation cascade triggered → May proceed to formation of FIBRIN → Disseminated intravascular coagulation (DIC) syndrome

Cellular metabolism



SHOCK

SEPTIC SHOCK (ENDOTOXIC)

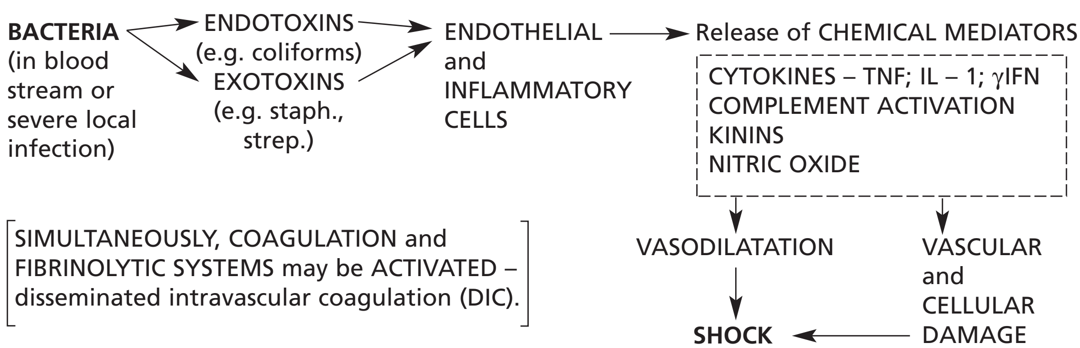
Causes

1. *Bacteria* – GRAM-NEGATIVE BACTERIA, especially the coliform group, are the commonest cause. They release endotoxin (lipopolysaccharide) from their cell wall when it is damaged. This toxin initiates cytokine cascades with the activation of damaging effectors including nitric oxide and platelet-activating factor. Other organisms can also produce shock, e.g. staphylococci, streptococci and meningococci. These produce exotoxins.

2. *Associated conditions*

(a) Serious primary bacterial infection, e.g. septicaemia, peritonitis – potentiated by deficiency in immune status (p.64) and liver disease where detoxification is impaired.
(b) Bacterial shock may complicate pre-existing shock due to other causes, e.g. burns.
(c) Bacterial shock may complicate relatively trivial surgical procedures, especially in the gastrointestinal and urinary tracts in the presence of infection.

Mechanism



SHOCK in BURNS and SCALDS

Mechanism

1. There is stimulation of afferent nerves, followed by;
2. An INFLAMMATORY RESPONSE evoked by the burned tissues.

Massive exudation and loss of PROTEIN-RICH fluid (sludging of blood in capillaries) → HYPOVOLAEMIA → SHOCK

The mechanism explains why the SEVERITY of the shock is roughly proportional to the exuding SURFACE AREA and not to the depth of the burn.

Other factors are chemical mediators derived from the burned tissues.

3. Complications which aggravate the shock:

(a) Infection: Burned tissues → Susceptible to infection esp. *Staph. aureus*, *Strep. pyogenes*, Gram-neg. bacilli (e.g. Pseudomonas) → SEPTIC SHOCK may be superimposed

(b) Anaemia: Haemolysis of red cells at burned site and later if sludging is severe → ANAEMIA

SHOCK – INDIVIDUAL ORGANS

HEART

There are two ways in which heart failure may be associated with shock.

1. In hypovolaemic and bacteraemic shock, heart failure is a *COMPLICATION*.

Mechanisms

Impaired respiratory function → HYPOXIA

Poor coronary circulation when BP falls to critical level → HYPOXIA

HYPOXIA → Depresses activity of myocardium

Chemicals released from damaged tissue (esp. pancreas) → Depresses activity of myocardium

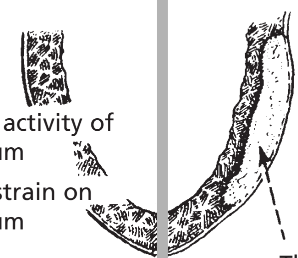
Peripheral vasoconstriction → Increases strain on myocardium → May be focal necrosis

2. In cardiogenic shock, acute heart failure is the *CAUSE* of shock.

Mechanism

Acute fall in cardiac output → Tissue HYPOXIA → SHOCK reaction → Further cardiac damage → Acute fall in cardiac output

Note: Venous return to heart (CVP) not reduced
Fluid replacement not required



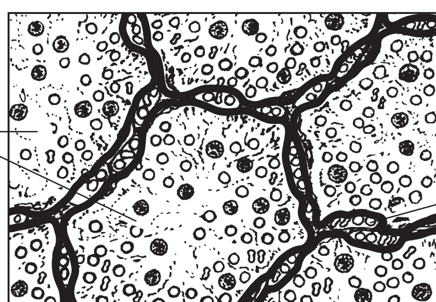
The commonest condition is myocardial infarction

LUNGS

Respiratory function is disturbed in 2 ways:

Circulatory changes in the lung (especially in septic/traumatic shock). These occur when compensatory mechanisms are failing. There is congestion and oedema, with the formation of hyaline membranes. At autopsy the lungs are heavy and wet. This condition is called 'shock lung' or adult respiratory distress syndrome (ARDS).

Early patchy changes throughout the lungs:



SHOCK – INDIVIDUAL ORGANS

KIDNEYS

The excretory function of the kidneys is always disturbed in shock. This is due to the general circulatory collapse and hypotension, but it may be aggravated by the secretion of renin and angiotensin by the kidney, aldosterone by the adrenal and antidiuretic hormone by the posterior pituitary. These hormones are secreted in an attempt to retain fluid and restore the blood volume, but by inducing vasoconstriction they will tend to increase renal damage.

Mechanism

FALL in BLOOD PRESSURE

INCREASING SEVERITY

→ Decreased GLOMERULAR FILTRATE (GF) → retention of → WASTE PRODUCTS (URAEMIA)

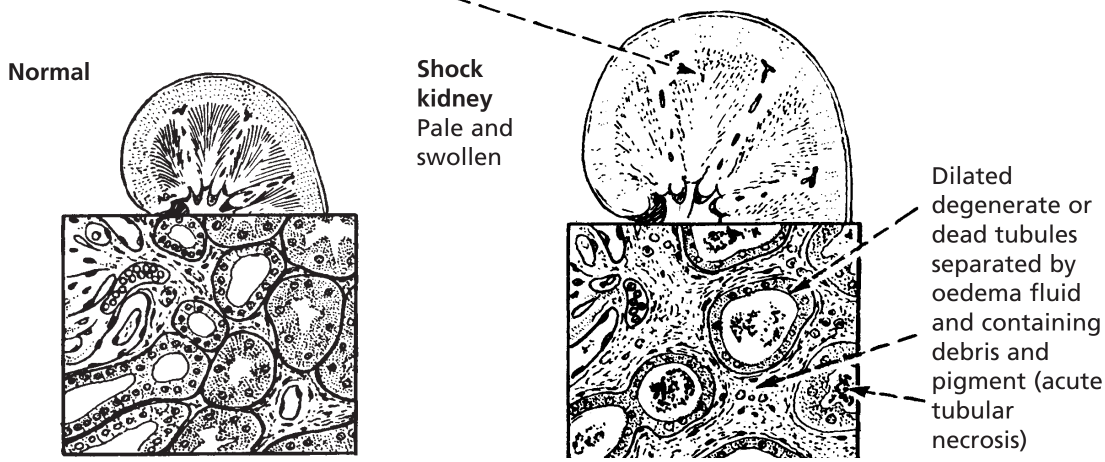
Increased breakdown of body proteins (esp. in traumatic shock) → Increased formation of → WASTE PRODUCTS (URAEMIA)

→ TUBULAR ischaemia (hypoxia)
Depression of function → (URAEMIA)
OLIGURIA (less than 400 ml urine/day)

→ TUBULAR NECROSIS
(esp. distal tubule: 'lower nephron')
GF completely reabsorbed
→ ANURIA (failure of urine formation: less than 100 ml/day) → SEVERE PROGRESSIVE URAEMIA

WASTE PRODUCTS (URAEMIA) → INCREASING SEVERITY → SEVERE PROGRESSIVE URAEMIA

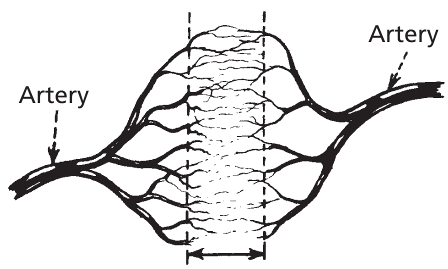
In such cases, at post mortem the kidneys are pale and swollen and the architectural markings are blurred

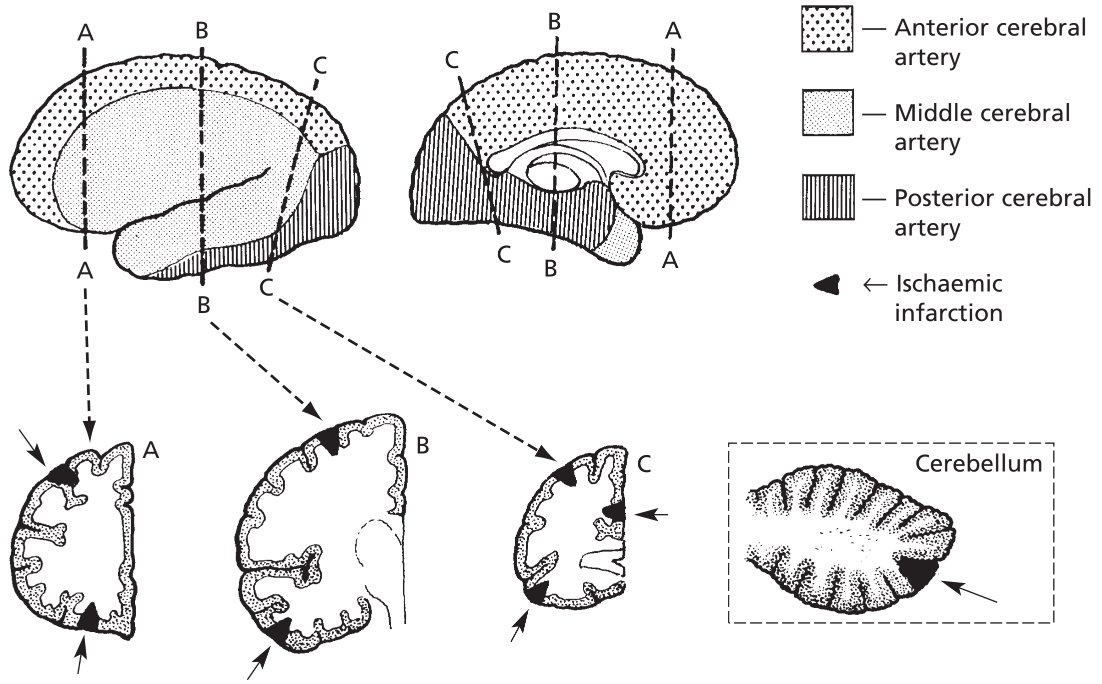


In even more severe shock the entire cortex may become necrotic (acute cortical necrosis).

SHOCK – INDIVIDUAL ORGANS

BRAIN
During the compensated phase of shock, relatively mild cerebral ischaemia is associated with changes in the state of consciousness. When the blood pressure falls to below 50–60 mmHg, the brain suffers serious ischaemic damage with infarction in the 'boundary zones' of the cerebral cortex and cerebellum.





There may also be more diffuse cerebral damage.

ALIMENTARY TRACT
In the stomach and duodenum there may be acute ulceration (Curling's or 'stress' ulcers) with perforation.

SHOCK – INDIVIDUAL ORGANS: OUTCOME

LIVER

The liver acinus is supplied by portal venous blood and hepatic arterial blood: in shock, Zone 3 of the hepatic acinus is vulnerable to anoxia.

Shock ⟶ reduced arterial blood supply ⟶ ANOXIA

May proceed to Zone 3 necrosis.

The OUTCOME of SHOCK

There are 3 possibilities, depending on several factors:

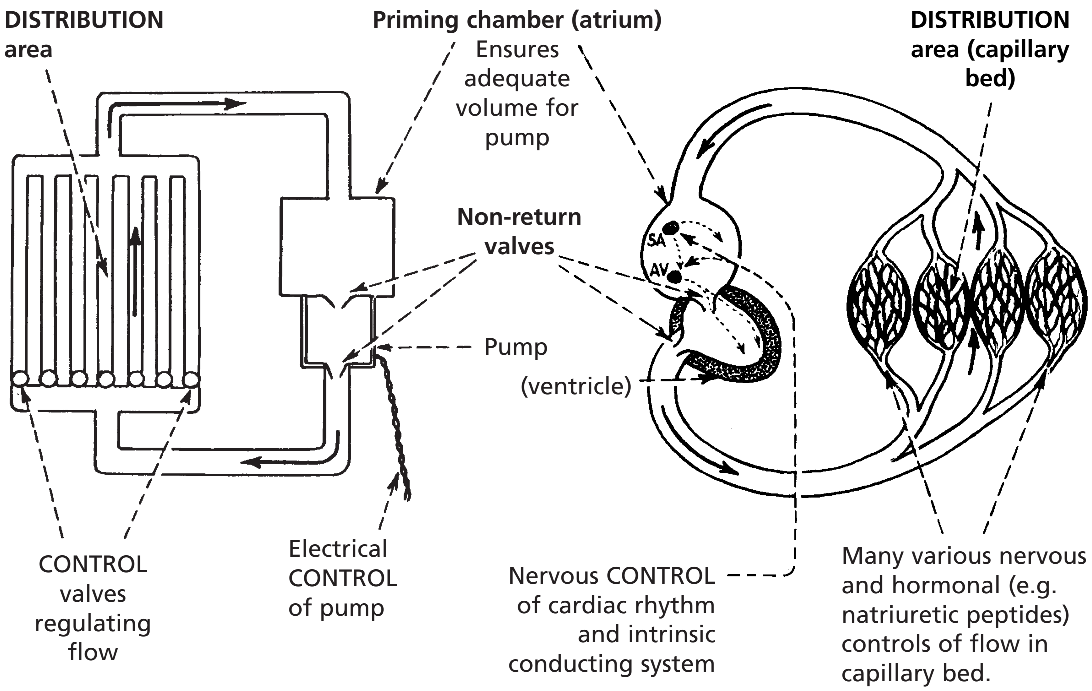
1. RECOVERY after convalescence, which may be long.
2. SURVIVAL with permanent damage to various organs.
3. DEATH

Factors favouring recovery	Factors favouring progression of shock
1. AVAILABILITY of EARLY TREATMENT of: (a) the INITIATING CAUSE (b) the HYPOVOLAEMIA 2. Youth 3. Good general health	1. DELAY in TREATMENT 2. FAILURE to REMOVE the INITIATING CAUSE 3. Old age 4. Poor general health 5. Pre-existing cardiovascular and lung disease 6. Onset of complications, esp. infection and organ damage

CARDIAC FUNCTION

The main function of the heart is to provide the pumping action in a closed circulation.

Comparison with a simple mechanical system is useful and valid provided that it is appreciated that the human heart is infinitely more sophisticated with delicate built-in controls and balances which influence the inotropic (intrinsic contractility) activity of the heart.



The pump is the essential part of the system: it has to be flexible to accommodate any changes required in the distribution side of the system.

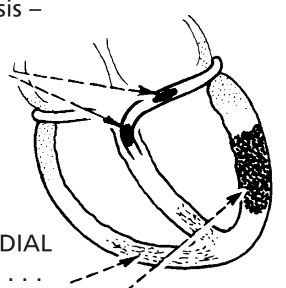
In the human circulation, reserves of ventricular muscle power are available to meet the wide range of metabolic activity required in the distribution area.

HEART FAILURE

Heart failure is very common and occurs when the ***ventricular muscle*** is incapable of maintaining a circulation adequate for the needs of the body, producing symptoms on exercise and at rest.

Causes of heart failure can be separated into two main groups:

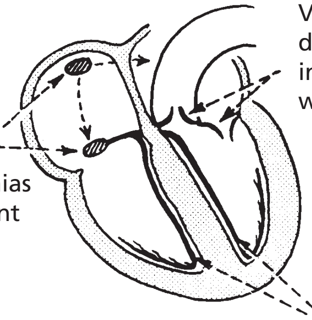
1. Diseases PRIMARILY affecting the MYOCARDIUM (PUMP)
(a) ISCHAEMIC HEART DISEASE
This is the most common and a very serious disease of the heart. The primary disease – atheroma and thrombosis – in the coronary arteries leads to



MYOCARDIAL DAMAGE . . .
. . . FIBROSIS or INFARCTION

(b) INFLAMMATION of the MYOCARDIUM (MYOCARDITIS)
(c) INFILTRATIONS of the MYOCARDIUM and CARDIOMYOPATHIES

2. Diseases of other cardiac and circulatory components leading secondarily to myocardial failure.
(a) CONTROL MECHANISM DEFECTS, i.e. CARDIAC ARRHYTHMIAS



(b) DISTRIBUTION DEFECTS

SYSTEMIC HYPERTENSION

Chronic lung disease causing pulmonary hypertension

Increased work load

LOSS OF MYOCARDIAL EFFICIENCY
INITIATION OF COMPENSATORY MECHANISMS

↓

FAILURE OF COMPENSATORY MECHANISMS

↓

Further LOSS OF MYOCARDIAL EFFICIENCY

↓

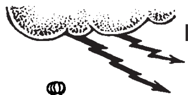
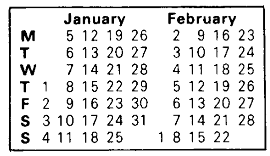
HEART FAILURE

HEART FAILURE

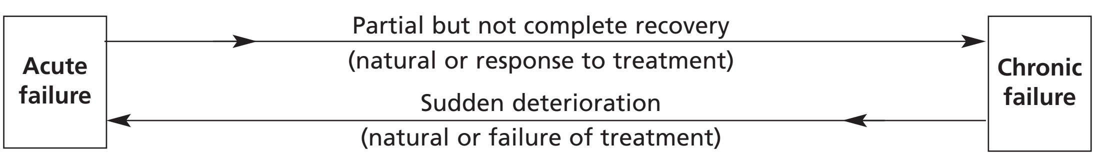
ACUTE and CHRONIC

This depends on the **suddenness of onset** and **rate of development.**

The causes and effects are different.

	Acute	Chronic
Time factors	 Instantaneous  Sudden (Hours – a few days)	 Weeks Months
Causes	(a) ACUTE CORONARY ARTERIAL OCCLUSION with infarction or arrhythmia (b) Pulmonary embolism (c) Severe malignant hypertension (d) Acute myocarditis (e) Acute valve rupture	(a) Ischaemic heart disease (b) Hypertension (c) Chronic valvular diseases (d) Chronic lung diseases (e) Chronic severe anaemia
Effects	SUDDEN DEATH May be no time for compensatory mechanisms to be initiated. Acute pulmonary oedema is common. May be acute ischaemic effects in brain and kidneys.	Compensatory mechanisms fully developed – hypertrophy and dilatation. Chronic oedema and chronic venous congestion.

Acute and chronic failure are at opposite ends of a spectrum but may merge.



HEART FAILURE

LEFT, RIGHT and COMBINED VENTRICULAR FAILURE

From a clinical point of view it is convenient to consider heart failure as affecting one or other side of the heart.

The pulmonary circulation
A low pressure system
Systolic arterial pressure = 24 mmHg
Pressure gradient, artery/vein = 8 mmHg

The systemic circulation
A high pressure system
Systolic arterial pressure = 120 mmHg
Pressure gradient, artery/vein = 90 mmHg

Right ventricular mass and coronary blood supply < Left ventricular mass and coronary blood supply
1:4 (approx.)

MAIN CAUSES OF:

Right ventricular failure

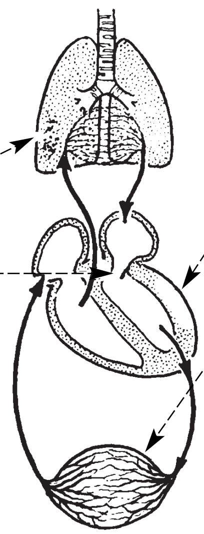
Usually secondary to disease elsewhere, causing obstruction to pulmonary blood flow.

(a) LUNG DISEASE
e.g. emphysema, fibrosis

(b) Some forms of cardiac valve disease, esp. MITRAL STENOSIS

(c) Congenital heart disease

(d) As a CONSEQUENCE of LV FAILURE



Left ventricular failure

1. Muscle weakness – ISCHAEMIC HEART DISEASE (due to coronary artery disease)
2. Excessive work load – SYSTEMIC HYPERTENSION

Since these causes are so prevalent, LV failure is much more common than RV failure.

Less common causes are:

Aortic valve disease
Mitral incompetence
Congenital heart disease.

Although left-sided and right-sided failure can occur independently, because their actions are closely integrated, failure of one cannot exist for long without eventually leading to failure of the other (combined ventricular failure).

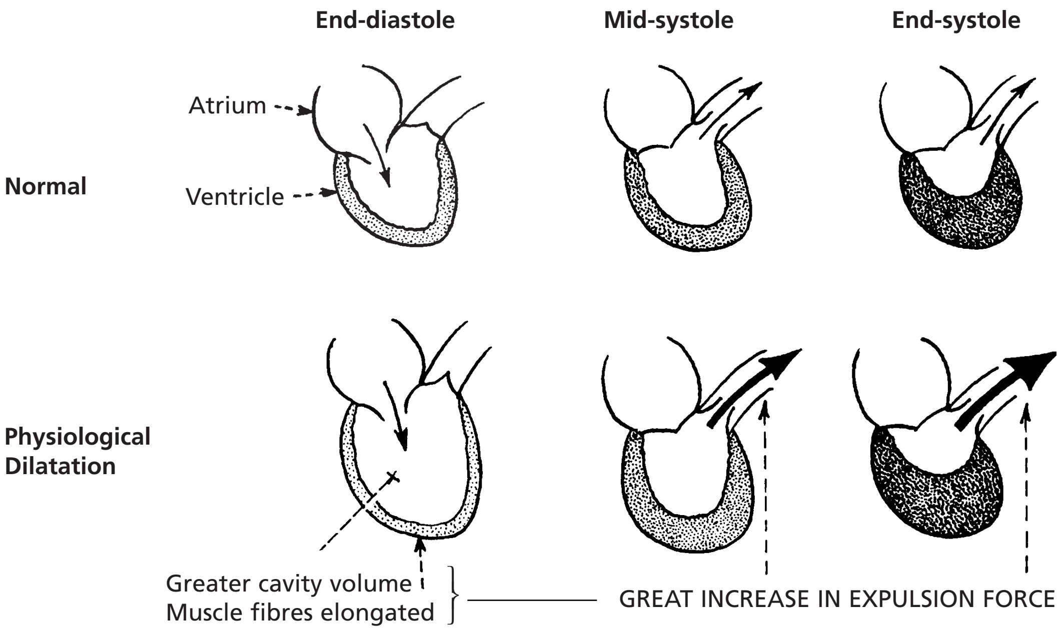
HEART FAILURE

COMPENSATORY MECHANISMS
The onset of heart failure is preceded by compensatory changes:

1. **Increased rate of pumping**
2. **Dilatation**
3. **Hypertrophy.**

DILATATION
In physiological conditions, the volume of the ventricular chamber at the end of diastole (pre-load) directly influences the pumping force of the ventricular muscle, therefore:

The larger the chamber size (i.e. the longer the initial fibre length and the greater the fibre stretch)	the greater the contracting force.



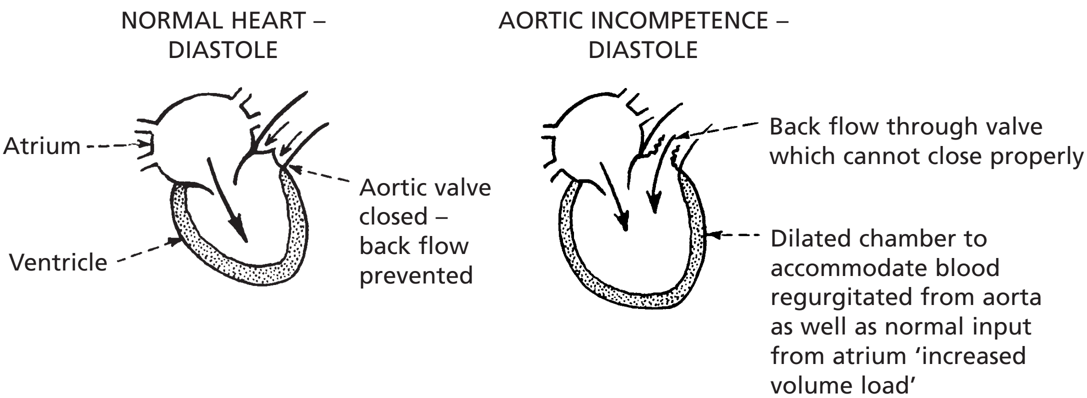
This physiological dilatation also occurs in cardiac disease.

HEART FAILURE

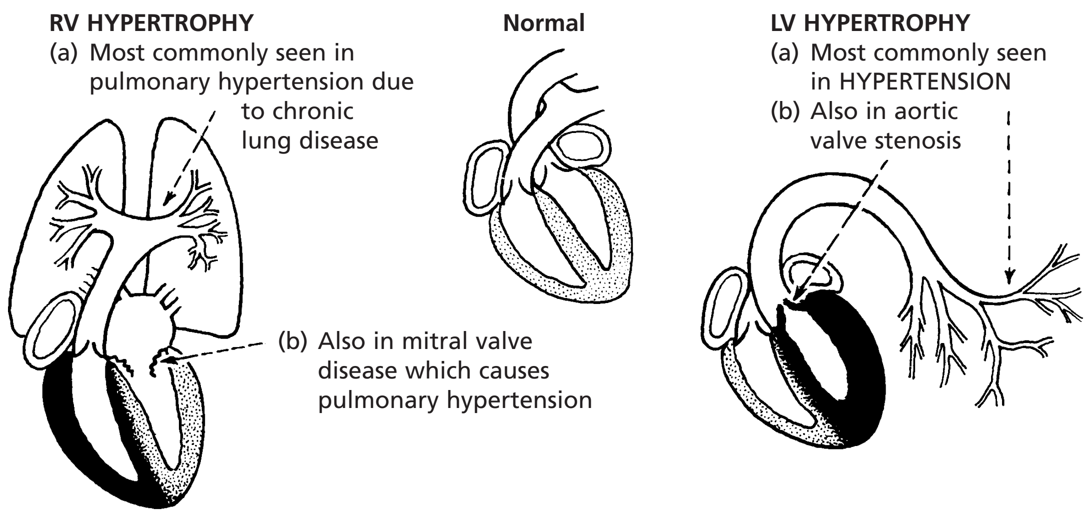
Compensatory Mechanisms – Dilatation *(continued)*

In cardiac disease, particularly in cases of valvular incompetence, dilatation which occurs passively to accommodate the regurgitated blood is an important factor.

Aortic valve incompetence is a good example:



HYPERTROPHY involves an increase in muscle fibre bulk; the increased muscle mass is able to deal with a greater work load. In its pure form, hypertrophy is seen best in cases of increased pressure load.



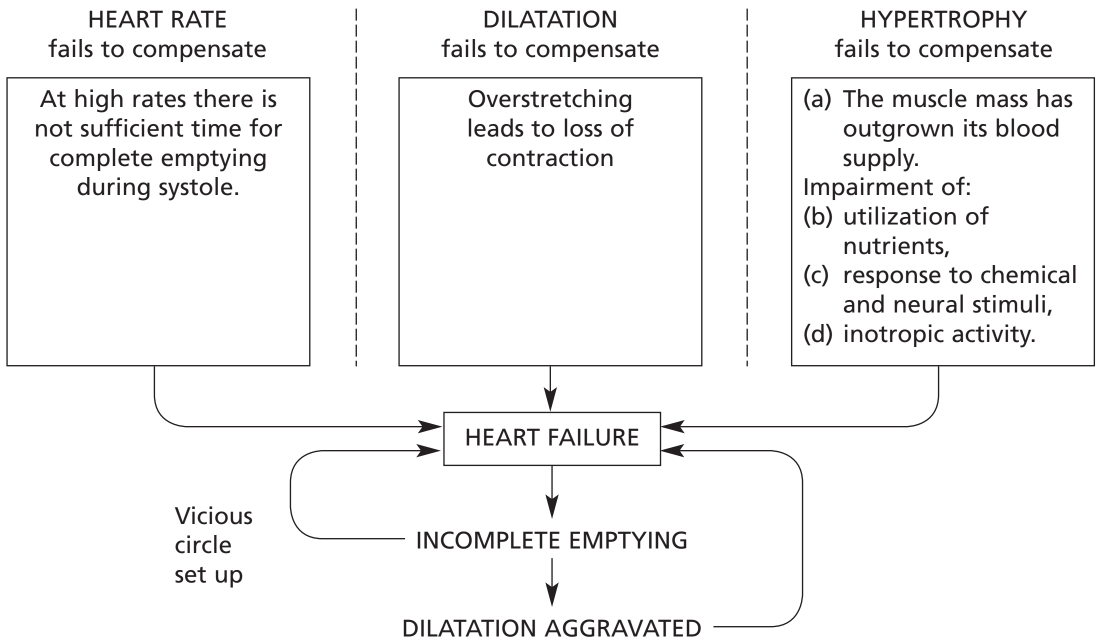
At first the blood supply to the hypertrophied muscle increases to meet the increased metabolic requirements. Later, however, the increased muscle bulk is detrimental as it places greater demands on the cardiac blood supply.

HEART FAILURE

FAILURE of COMPENSATORY MECHANISMS

The increased efficiency derived from all three mechanisms is limited, and beyond this limit heart failure develops.

Beyond the critical limit:



Thus in most cases of heart failure there is CARDIAC ENLARGEMENT due usually to a combination of hypertrophy and dilatation.

The **effects** and **symptoms** of heart failure are seen in the peripheral organs and are due to HYPOXIA and VENOUS CONGESTION.

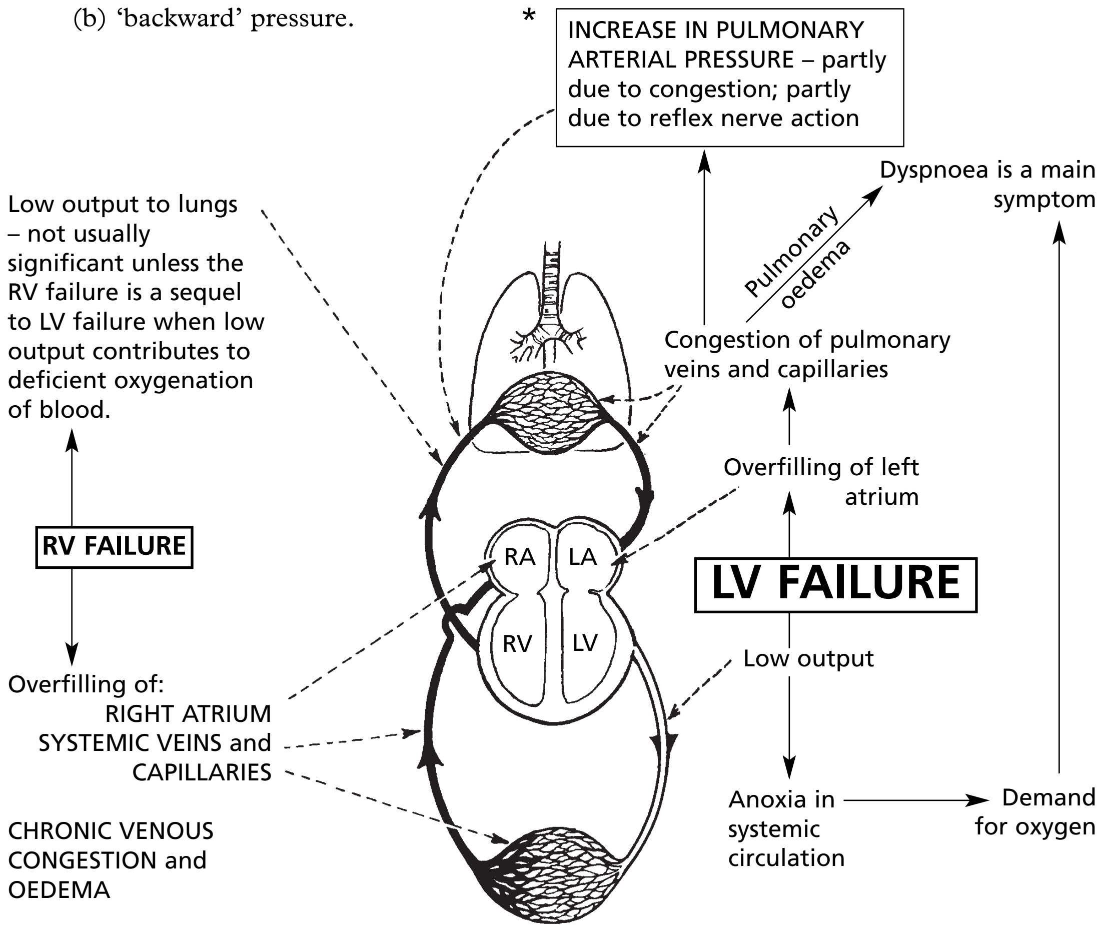
(a) In the chronic forms of heart failure, the **weakness and fatigue** are due mainly to **hypoxy**.

(b) Venous congestion and oedema are important.
Breathlessness (dyspnoea) is almost a constant feature of heart failure and is due to venous congestion and fluid retention within the lungs.
In severe failure, particularly when bed rest is obligatory, *hypostatic pneumonia* and *pulmonary embolism* (from leg vein thrombosis) may be serious and terminal complications.

EFFECTS OF HEART FAILURE

Left ventricular failure is the initiating event in most cases of combined failure.

The main effects are the results of:
- (a) low output
- (b) 'backward' pressure.



Cyanosis is the result of excess reduced haemoglobin in capillaries and venules.

* The increase in pulmonary arterial pressure is important because in most cases of chronic LV failure it eventually leads to RV failure (combined failure).

ACUTE PULMONARY OEDEMA

In **acute left ventricular failure**, accumulation of fluid results in dyspnoea and hypoxaemia.

↓ left ventricular output
↓
pulmonary venous pressure ↑
↓
↑ fluid in alveolar walls - - → ↓ lung compliance
↓
↑ fluid in alveolar spaces - - → pink frothy sputum
↓
IMPAIRED GAS EXCHANGE

CHRONIC VENOUS CONGESTION of the LUNGS

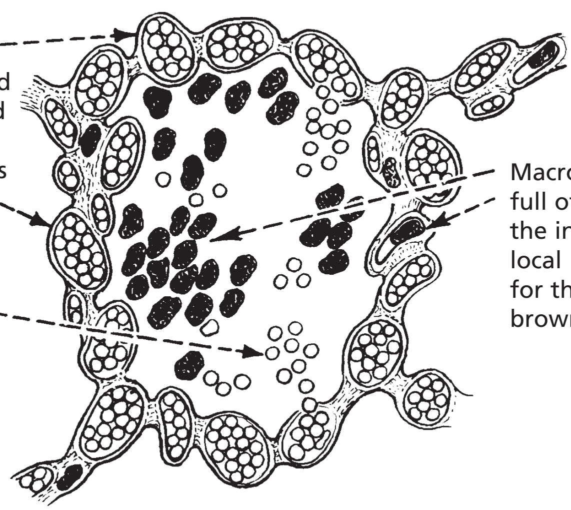
The results of chronic combined (congestive) failure and/or chronic left ventricular failure:

The lungs are bulky, congested and brownish in colour.

Cardiac failure → Hypoxia → Hyperventilation

Cardiac failure → Pulmonary venous engorgement → Pulmonary oedema

Pulmonary venous engorgement → Alveolar haemorrhage → Breakdown of haemoglobin to haemosiderin and bilirubin



HEART FAILURE

CHRONIC VENOUS CONGESTION

Congestion of the systemic venous circulation is a result of right heart failure whether secondary to left heart failure or lung disease (cor pulmonale).

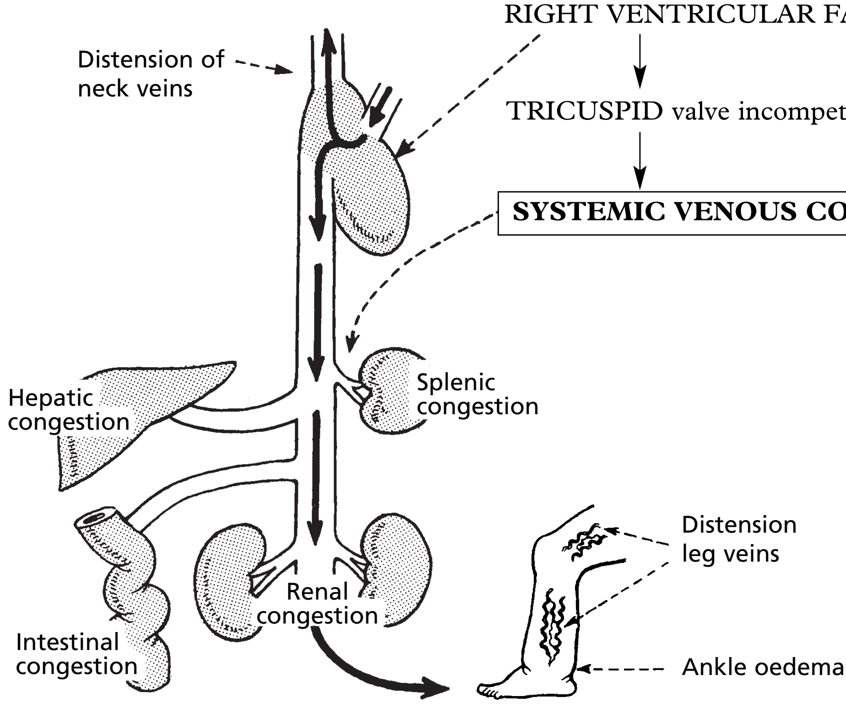
The basic mechanism is:

CHRONIC CARDIAC FAILURE → REDUCED left ventricular output + MITRAL valve incompetence → chronic PULMONARY VENOUS CONGESTION + increased pulmonary arterial pressure → RIGHT VENTRICULAR FAILURE

LUNG DISEASE → increased pulmonary vascular resistance → RIGHT VENTRICULAR FAILURE

RIGHT VENTRICULAR FAILURE → TRICUSPID valve incompetence → **SYSTEMIC VENOUS CONGESTION**

RIGHT VENTRICULAR FAILURE → **SYSTEMIC VENOUS CONGESTION**



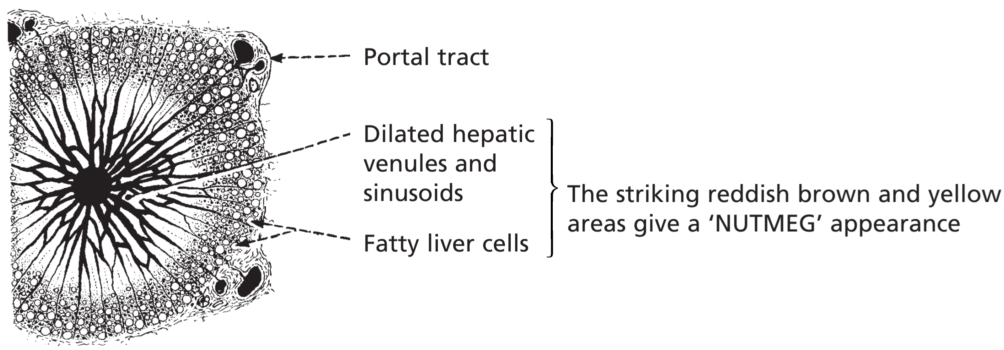
Pleural effusion is also a common effect (see p.282).

HEART FAILURE

CHRONIC VENOUS CONGESTION *(continued)*

The **liver** shows striking changes: Distension of the veins causes enlargement of the liver so that it can be felt below the costal margin.

The parenchymal cells furthest from the arterial blood supply, i.e. around the hepatic venules, undergo degeneration with atrophy and ultimately disappear. Cells nearer the arteries show an accumulation of fat.



FLUID RETENTION

This is related to the REDUCED OUTPUT from the LEFT VENTRICLE: the mechanism involves retention of sodium and water.

Reduced LV output → renin released → angiotensin is activated

Reduced LV output ↓ Reduced KIDNEY perfusion ↓ Fall in glomerular filtration ↘

angiotensin is activated ↓ adrenal cortex stimulated ↓ aldosterone secreted ↙

RETENTION of SODIUM and WATER

↓

contributes to OEDEMA – for which there are 2 main mechanisms in heart failure:

1. Overfilling of venules ↓ Increased hydrostatic pressure ↘

2. Retention of water and electrolytes ↓ Increased total body fluid ↙

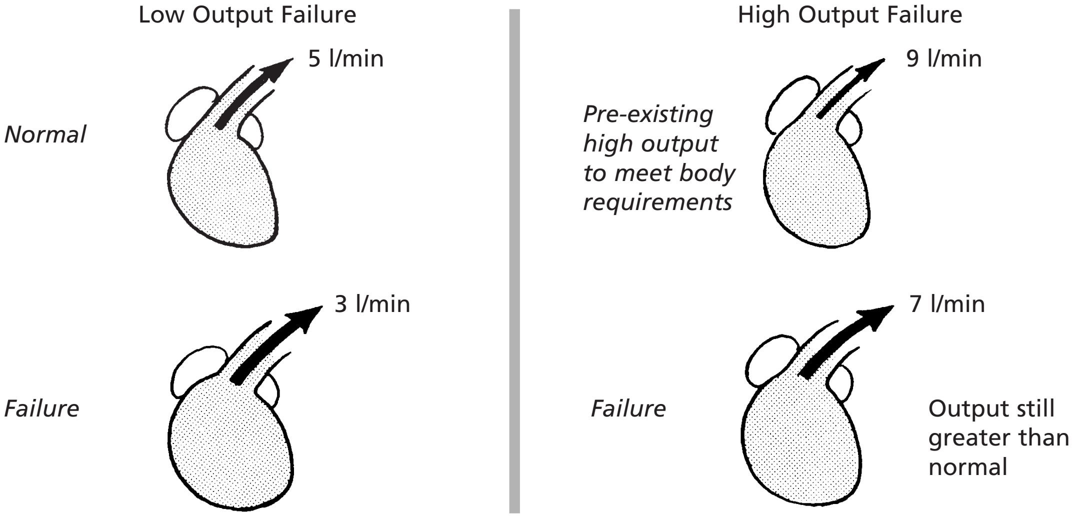
Oedema of dependent parts where pressure is greatest

Pleural effusion (p.282) and ascites (p.169) are also common effects of fluid retention in congestive cardiac failure.

HIGH OUTPUT CARDIAC FAILURE

LOW and HIGH OUTPUT FAILURE
By definition, in cardiac failure, output is low in respect of body requirements, and in most cases this output is lower than the usual normal output. Such cases are called **Low Output type.**

In a few conditions, the cardiac failure complicates a pre-existing state in which the output before failure was greater than normal. In these cases, the output is not sufficient to meet the body requirements but may still be higher than the normal. Such cases are called **High Output type.**



Causes
The common types of failure:

HYPERTENSIVE HEART DISEASE
ISCHAEMIC HEART DISEASE
VALVULAR HEART DISEASE
MYOCARDITIS.

Diseases associated with increased blood volume:

CHRONIC ANAEMIA
ARTERIOVENOUS SHUNTING
HYPERTHYROIDISM
SEVERE ANAEMIA.

In both types of failure, venous overfilling is an important sign, but in high output failure venous overfilling is usually present before failure ensues, reflecting the increased blood volume.

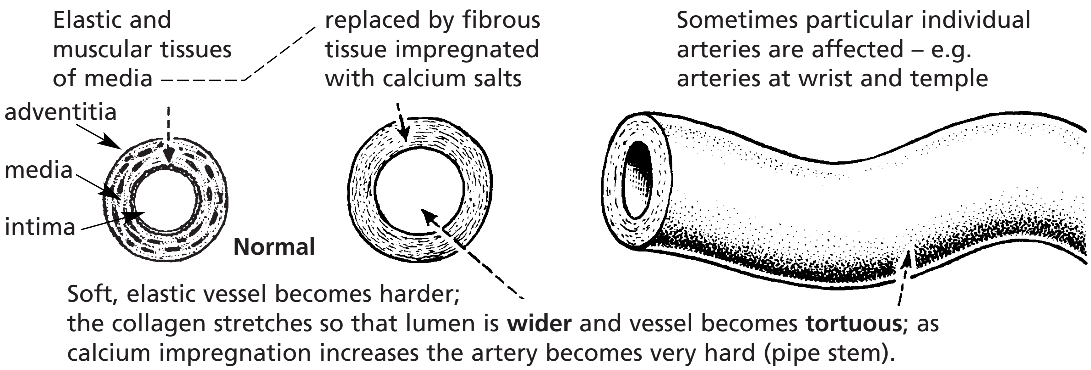
DISEASES OF ARTERIES – ARTERIOSCLEROSIS

Arterial diseases are very common and are important because of their serious effects, especially on the heart and brain.

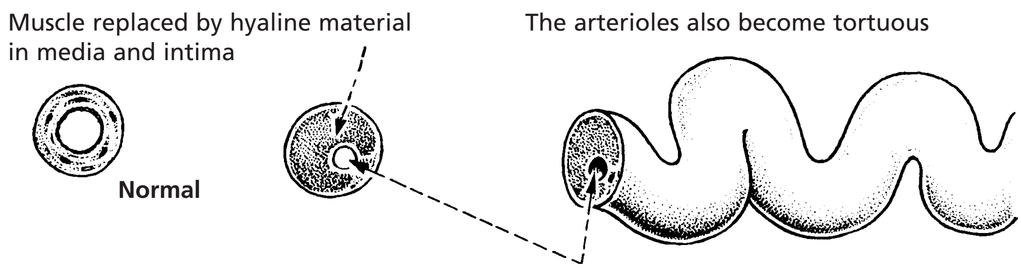
Normal age related vascular changes:

ARTERIOSCLEROSIS (hardening of the arteries)

This is a generalised degeneration of the specialised muscle and elastic tissue of the media of the vessel wall, and replacement by fibrous tissue, proteoglycan and calcium salts. There is also proliferation of the inner layer of the vessel (intima).



HYALINE ARTERIOLOSCLEROSIS affects the small branches of the arterial system (arterioles) – especially in the kidney.



This is due to entry of blood plasma under the endothelium with protein deposition; gradual replacement by collagen occurs. The process is called **plasmatic vasculosis**.

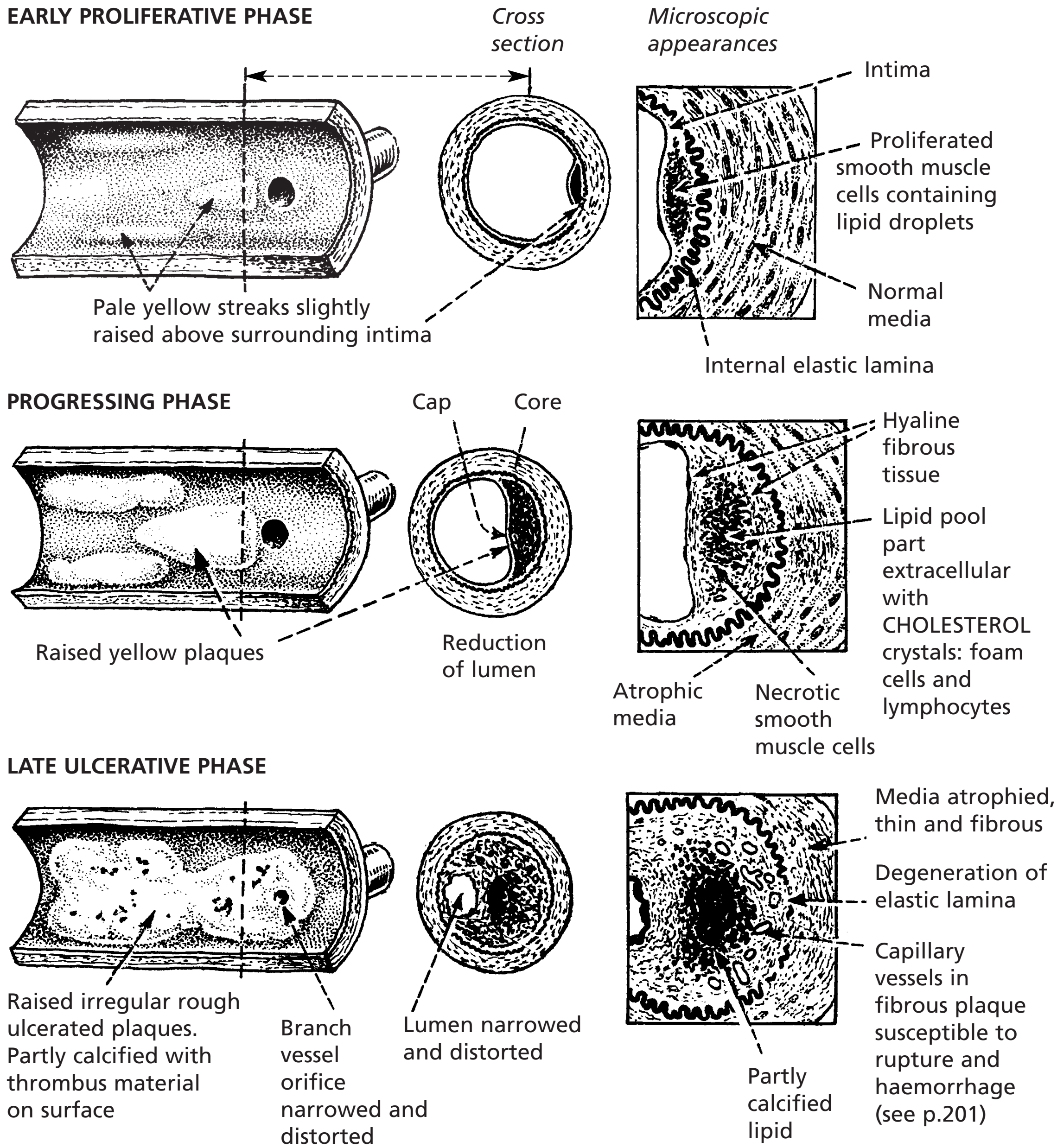
Note: Arteriosclerosis is aggravated by HYPERTENSION and DIABETES MELLITUS.

In a variant of arteriosclerosis (Monckeberg), seen in the very elderly, calcium salts are very heavily deposited in the media particularly of the leg arteries. The X-ray appearances are striking but there is no significant loss of lumen unless atheroma co-exists.

ATHEROMA (ATHEROSCLEROSIS)

Atheroma is a common disease in Westernised countries, it is of gradual onset but is progressive. It is commonly seen in the middle aged and elderly but the earliest changes are present in adolescents. It is often asymptomatic but it may cause serious disease or death from complicating thrombosis. The lesions represent patchy deposition of lipid within plaques deep in the intima.

(Vessel opened longitudinally)

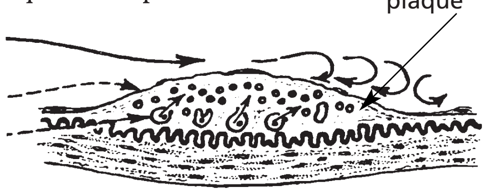


ATHEROMA – COMPLICATIONS

Fibrosis in the intima and media weaken the wall and may lead to aneurysm formation (see p.231), but the most important complication of atheroma is THROMBOSIS.

Local factors at the site of the atheromatous plaque are important:

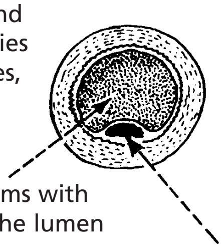
1. Intimal roughening or distortion with eddying of flow
2. Thin, easily damaged intimal surface
3. Rupture of new capillaries in plaque with haemorrhage into the plaque.



In addition, general factors influencing blood coagulability are important, e.g. smoking affecting vessel contractility and platelet function.

Results

1. Medium and small arteries – coronaries, cerebrals



2. Larger arteries – aorta, carotids. Lumen usually too large to be completely occluded



The important sites of atheroma and the effects due to complications are:

CEREBRALS (Circle of Willis or branches) CAROTIDS	**Acute local ischaemia** – cerebral infarction (stroke) Chronic ischaemia of brain – multi-infarct dementia
CORONARIES	**Acute infarction** **Chronic ischaemia of myocardium with fibrosis**
ABDOMINAL AORTA	**Aneurysm** – embolism to legs
RENAL ARTERIES	**Chronic ischaemia of kidneys**
Visceral arteries	Acute or chronic ischaemia of bowel
Lower limb arteries (Upper limb arteries are rarely affected)	With severe atheroma, chronic ischaemia with claudication occurs and gangrene may develop.

In severe cases of atheroma, most of these sites may be affected.

ATHEROMA – AETIOLOGY

The cause of atheroma is complex and multifactorial. There are many risk factors, the HEAVY SMOKING, HYPERTENSIVE, OBESE, SEDENTARY MALE.



The various risk factors exponentially increase with AGE. They are considered in 3 groups:

1. **ENDOGENOUS**
   - (a) *SEX* – male > female
   - (b) *HEREDITY*
     - (i) Family history of premature heart disease
     - (ii) Familial hyperlipidaemias

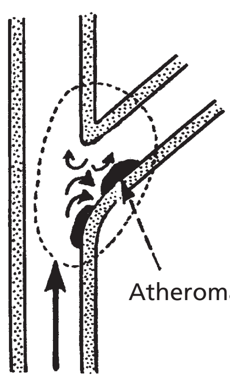
   Increased plasma cholesterol is an important risk factor and the ratio of low density lipoprotein (LDL) to high density lipoprotein (HDL) especially, so: LDL↑ risk↑↑
   HDL↑ risk↓.

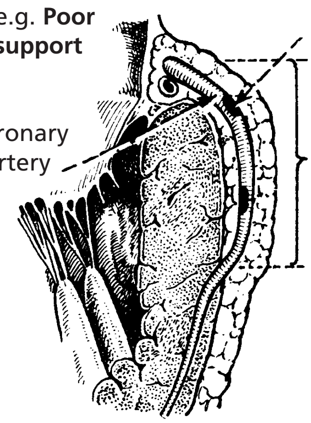
2. **ENVIRONMENTAL**
   - (a) *SMOKING*
   - (b) *DIET* – rich in saturated fats and cholesterol and low in fruit and vegetables
   - (c) Lack of exercise
   - (d) Low socio-economic group status.

3. **DISEASES**
   - (a) *HYPERTENSION*
   - (b) Hyperlipidaemia
   - (c) Diabetes Mellitus
   - (d) Obesity
   - (e) Increased fibrinogen levels.

Modification of some of these risk factors has led to a fall in incidence especially in higher socio-economic groups. Avoiding smoking, dietary improvement and exercise seem most important, while treating raised cholesterol with statins is now widely used.

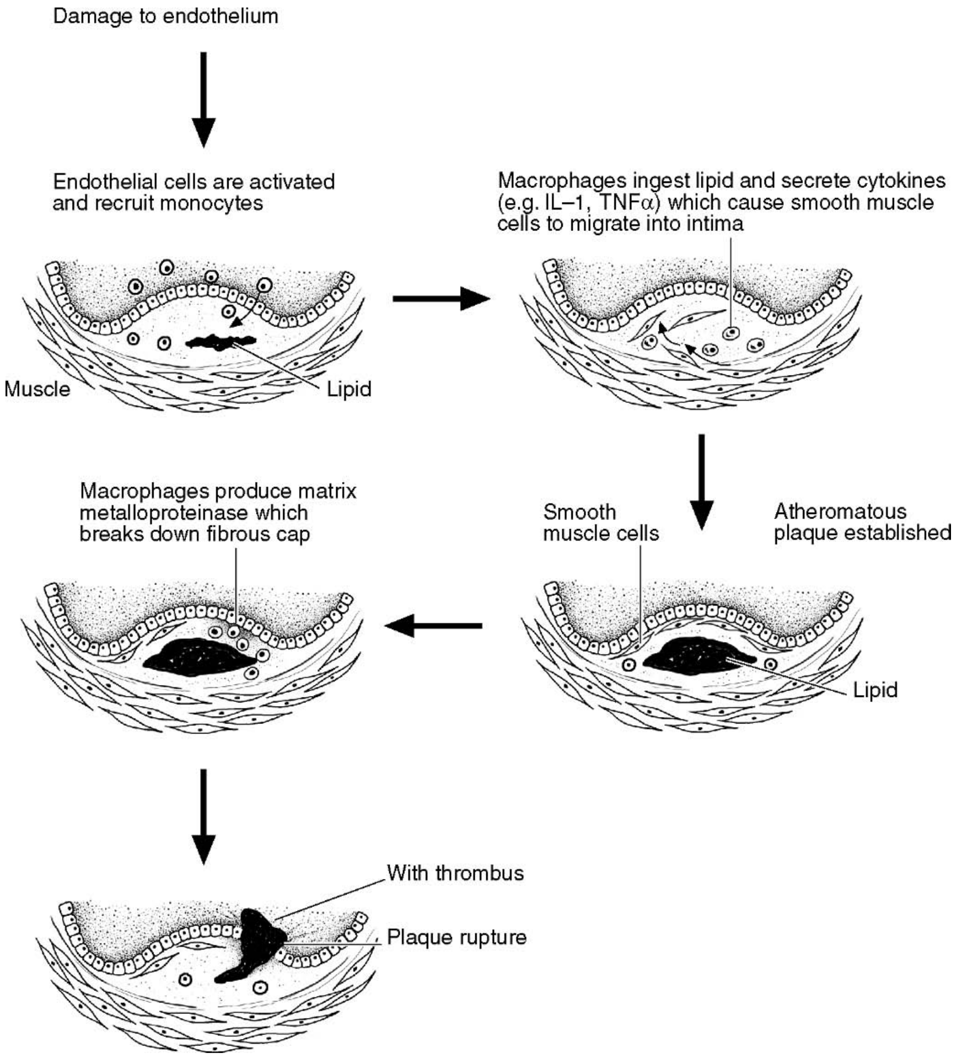
PATHOGENESIS OF ATHEROSCLEROSIS
Endothelial Damage
Atheroma is now regarded as an inflammatory disease of the arterial wall initiated by same form of injury to the endothelium. Evidence for this includes the preferential distribution of lesions, e.g. arch of aorta, coronary arteries, cerebral arteries, carotids, abdominal aorta where local mechanical stress is common.





ATHEROMA – AETIOLOGY AND PROGRESSION

Pathogenesis



HYPERTENSION

High blood pressure (BP) is important because it increases the risk of cardiovascular disease, especially:

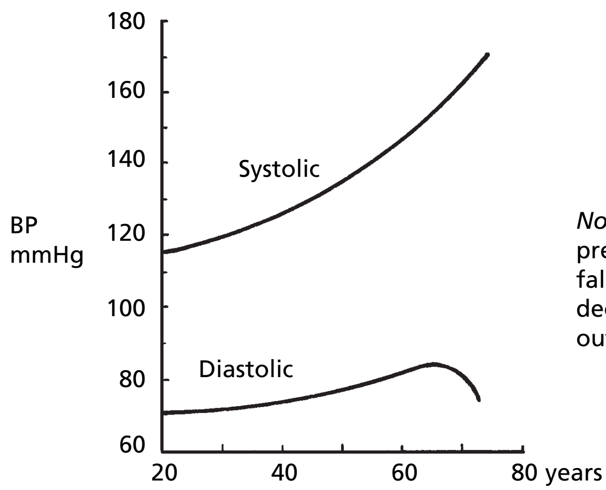
1. **Left Ventricular Hypertrophy** } → Cardiac failure.
2. **Ischaemic Heart Disease** } → Sudden death.
3. **Stroke** – Cerebral haemorrhage or Infarction.

Blood pressure is a continuous variable within the population. It is determined essentially by 2 variables:

BLOOD PRESSURE = CARDIAC OUTPUT × TOTAL PERIPHERAL RESISTANCE.

Mechanisms of normal maintenance of BP and the effect of age

The systolic pressure is governed by (a) cardiac action (b) the ELASTICITY and DISTENSIBILITY of the CONDUCTING ARTERIES.	Increasing AGE is normally associated with ARTERIOSCLEROSIS – loss of distensibility →	∴ Increased SYSTOLIC pressure
The diastolic pressure is maintained by the **RESISTANCE (TONE)** of arterioles (a subsidiary factor is blood viscosity)	ARTERIOLOSCLEROSIS – increased resistance →	∴ Increased DIASTOLIC pressure



Note: Diastolic pressure tends to fall after the 7th decade as cardiac output falls.

Because of the wide range in the normal population, the definition of high BP is arbitrary. The risk of complications progressively increases with BP, including within the normal range. The levels of **systolic** and **diastolic** pressure are both risk factors.

Systolic BP > 160 mmHg and Diastolic BP > 95 are generally accepted as **Hypertension**.

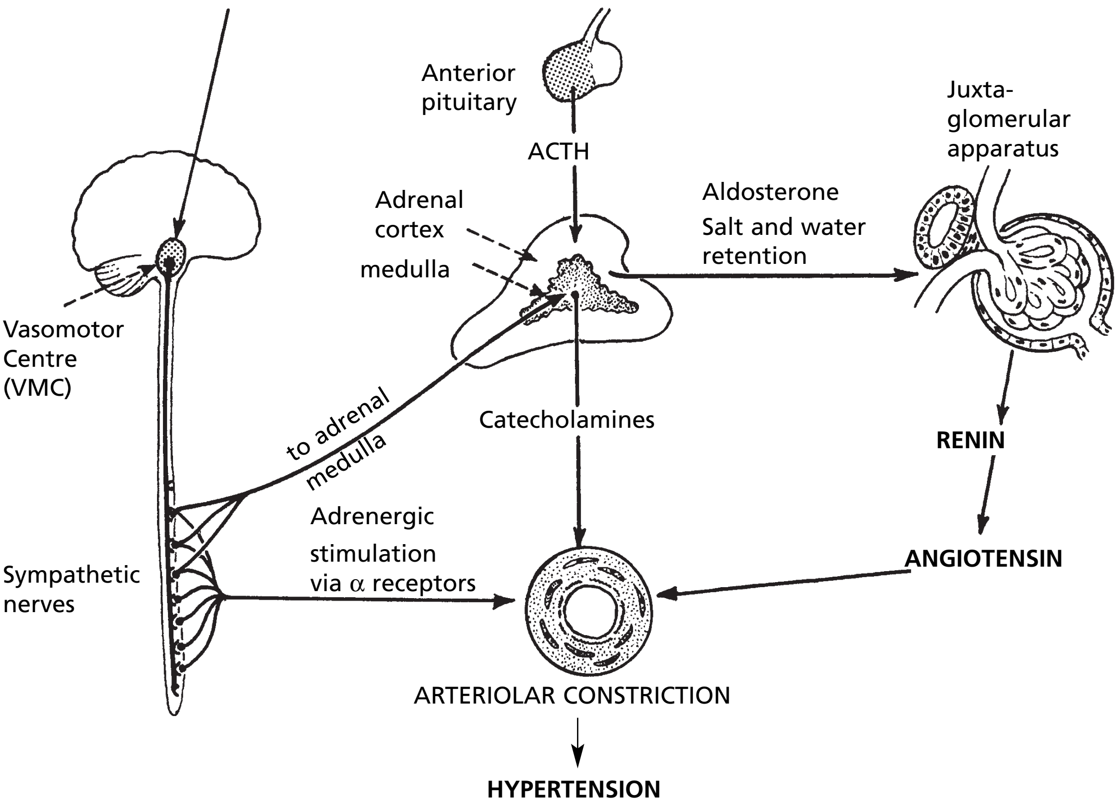
Modern therapy is effective in lowering BP. The decision whether or not to treat depends on the level of BP and the presence of other risk factors for cardiovascular disease.

HYPERTENSION

Aetiology
The following diagram illustrates the physiological mechanisms controlling Blood Pressure. They are presented in 2 groups but are complex and interconnected with feed-back controls.

1. **Autonomic Nervous System**
   (a) External environment
   (b) Internal environment, e.g. baroreceptors

2. **Hormones**
   (a) Pituitary/Adrenal
   (b) Renal



Note: **Nitric oxide** (NO) and **Endothelin** are both produced physiologically by endothelial cells. They have powerful and opposite effects.

Nitric oxide ——— vasodilatation (short-acting).
Endothelin ——— vasoconstriction (long-acting).

Their role in hypertension is not yet clear.

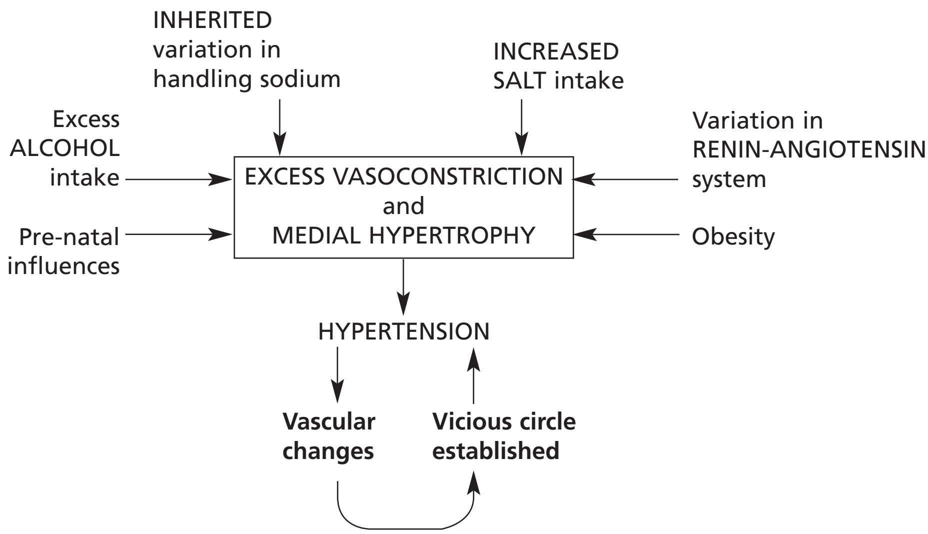
HYPERTENSION – ESSENTIAL AND SECONDARY

ESSENTIAL HYPERTENSION

In 95% of cases of hypertension no obvious cause is found – this is ESSENTIAL hypertension – (a diagnosis of exclusion).

A number of aetiological factors may be implicated:

1. Genetic predisposition – polygenic inheritance.
2. Racial, e.g. black > white.
3. Sodium homeostasis: increased **salt intake.**
4. Lack of exercise.



SECONDARY HYPERTENSION

5% of hypertension is a complication of other diseases. They are broadly classified as:

(a) *Kidney diseases* e.g. chronic renal failure, renal artery stenosis, polycystic kidneys. The mechanism is usually renal ischaemia with activation of the renin-angiotensin system.

(b) *Endocrine disorders* – Cushing's syndrome – corticosteroid excess;
Conn's syndrome – aldosterone excess;
Phaeochromocytoma – catecholamine excess.

(c) *Coarctation of aorta* – aortic narrowing → renal perfusion impaired → renin-angiotensin activation.

(d) *Eclampsia* and pre-eclampsia in pregnancy.

(e) *Drugs* e.g. steroids: oral contraceptives.

HYPERTENSION – ESSENTIAL AND SECONDARY

CLASSIFICATION – BENIGN AND MALIGNANT

In the classification of hypertension, in addition to the aetiology, two other main factors are considered.

1. **Rate of Progress**		2. **Height and rapidity of rise of the BP**	
Chronic – over many years	+	Usually only mild or moderate very slow rise. (*Note:* The very old may have considerably higher BP without ill-effects)	**Benign** – during long course but eventually may have serious effects
Rapid (acute) – months or 1–2 years	+	Usually very high and rapidly rising BP, e.g. 120 + diastolic	**Malignant** – serious damaging effects

Summary

Essential (95%): Benign or Malignant

Secondary (5%): Benign or Malignant

COMPARISON of BENIGN and MALIGNANT HYPERTENSION

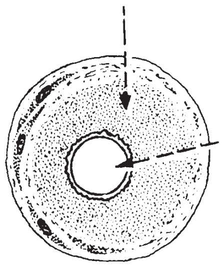
	Benign	Malignant
Aetiology	Usually ESSENTIAL If secondary, commonly of endocrine type	A few cases arise from benign essential. Majority are SECONDARY TO RENAL DISEASE
Age	Begins younger than 45 years but is prolonged into 6 and 7 decades	Young adults 25–35 years
Sex	Female > Male	Female = Male
Prevalence	VERY COMMON – at least 15% of population in Western societies	Rare
Course	VERY SLOW – many years	RAPID – months to 1–2 years
Blood pressure	Diastolic 90–120 mmHg Very slow rise	Diastolic >120 mmHg Rapid rise

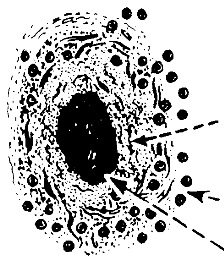
HYPERTENSION

COMPARISON of BENIGN and MALIGNANT HYPERTENSION *(continued)*

VASCULAR CHANGES

	Benign	Malignant
Arteries	Accelerates ARTERIOSCLEROSIS; POTENTIATES ATHEROMA	Accelerates arteriosclerosis; causes INTIMAL FIBROUS THICKENING
Arterioles	Hyaline thickening "plasmatic vasculosis"	FIBRINOID necrosis of vessel wall and thrombosis, especially affecting kidney and abdominal viscera





EFFECTS and MAIN COMPLICATIONS in VARIOUS ORGANS

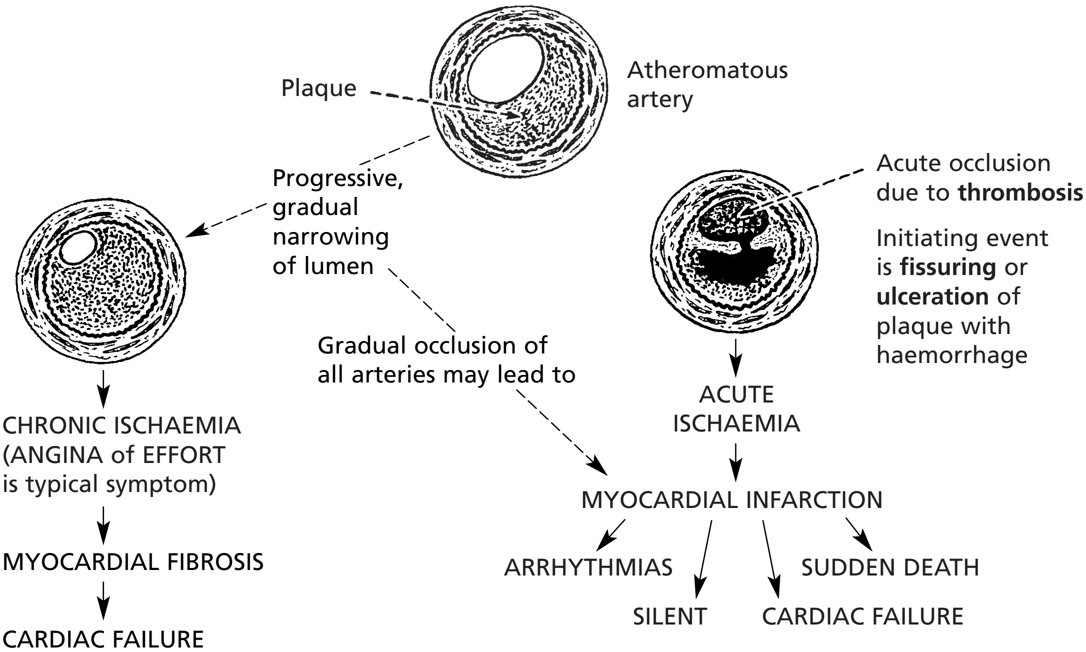
	Benign	Malignant
Heart	Hypertrophy of left ventricle	Hypertrophy of left ventricle ± focal myocardial necrosis
Heart failure	Common	Acute heart failure
Cerebral haemorrhage	Due to rupture of damaged artery	Encephalopathy (fits and loss of consciousness) due to cerebral oedema and haemorrhage
Kidney	Varying degrees of NEPHROSCLEROSIS but usually *not* serious	Severe renal damage – death in uraemia
Eyes	Arterial narrowing – retinal exudation.	Papilloedema; arterial narrowing; haemorrhage and exudates.

The effects and complications are proportional to the height of the blood pressure. Therefore drug treatment which lowers the BP lowers the incidence of complications, but the diseased vessels do not return to normal and organ perfusion may be inadequate at levels of BP which would usually be considered physiological.

Note: Modern drug therapy has greatly reduced the morbidity and mortality from malignant hypertension.

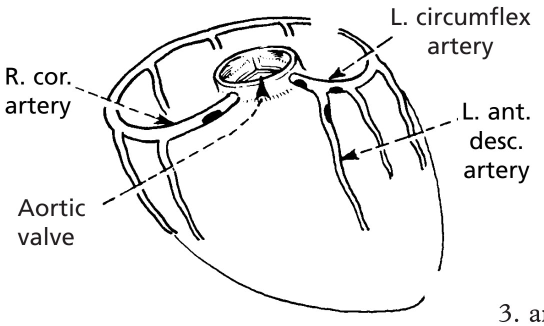
ISCHAEMIC HEART DISEASE

Cardiac ischaemia is the major cause of death in affluent Western societies. It is almost always due to **atheroma** of the **coronary arteries** causing narrowing or occlusion. The effects may be sudden or of gradual onset.

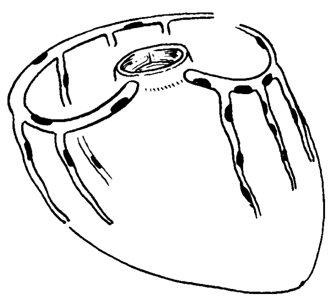


Distribution of atheromatous plaques

1. There may be only a few plaques, but because the sites of predilection are in the proximal parts of the arteries (usually within 3 cm of the origin from the aorta), the effects of occlusion are serious.



or 2. Very numerous plaques.
Note: The small terminal arteries penetrating the myocardium are usually not affected.



3. any combination of 1. and 2.

The site of ischaemic damage usually represents the distribution area of the diseased arterial branch.

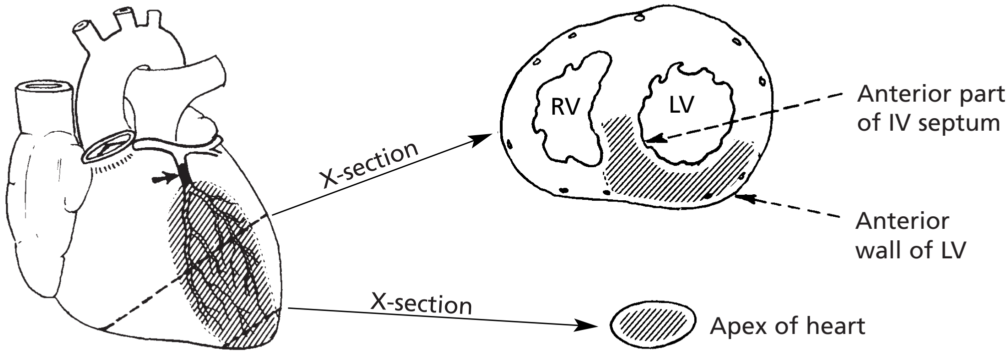
MYOCARDIAL INFARCTION

90% of cardiac infarcts are regional in distribution. The remaining 10% are subendocardial.

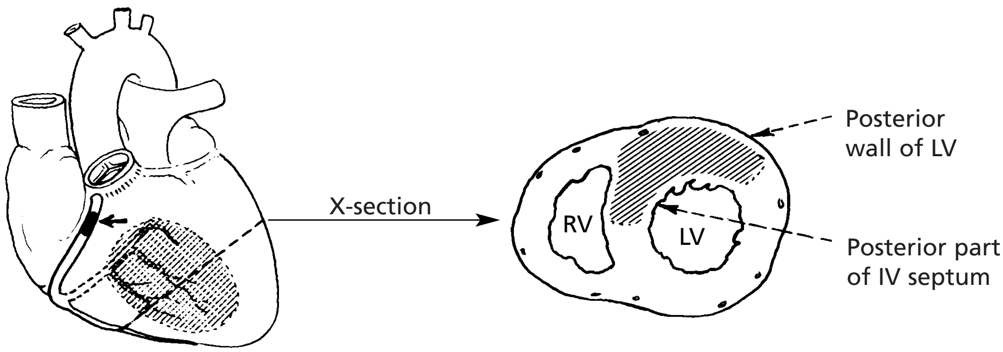
REGIONAL INFARCTION

The three commonest regions are:

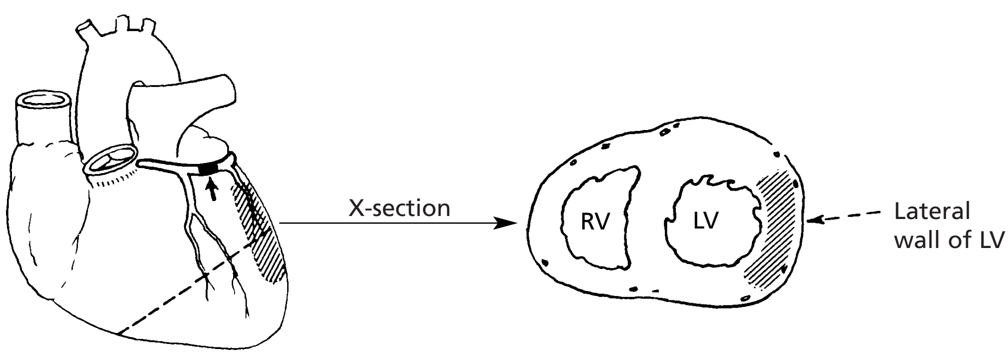
1. LEFT CORONARY ARTERY – ANTERIOR DESCENDING BRANCH



2. RIGHT CORONARY ARTERY



3. LEFT CORONARY ARTERY – CIRCUMFLEX BRANCH

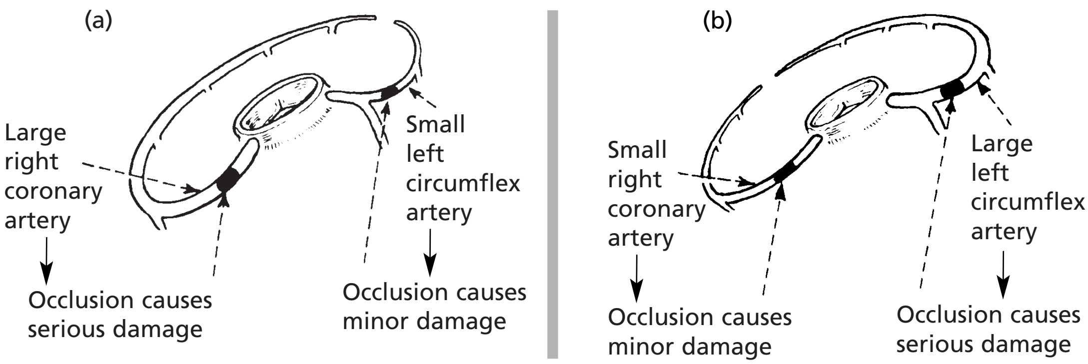


MYOCARDIAL INFARCTION

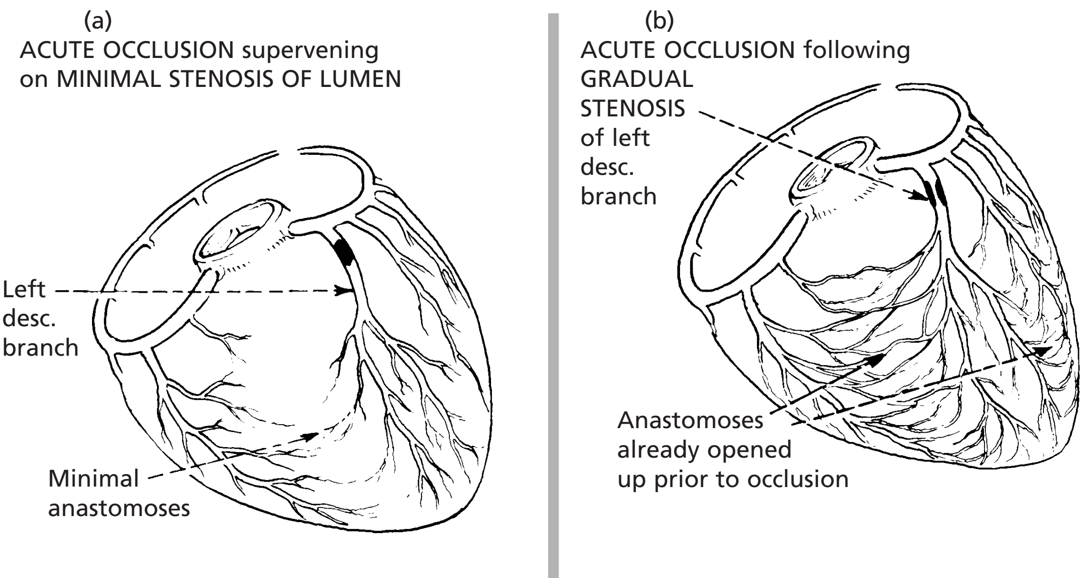
EXTENT OF DAMAGE

This depends on:

1. The inherited individual anatomical variation in distribution area, e.g. the calibres of the right coronary artery and the circumflex branch of the left coronary artery show considerable variation and are usually inversely related.



2. The efficiency of any anastomosis in the deprived distribution area. Gradual narrowing of an artery allows time for increased anastomosis to the deprived distribution area to develop, and so old age tends to be associated with improved anastomoses.



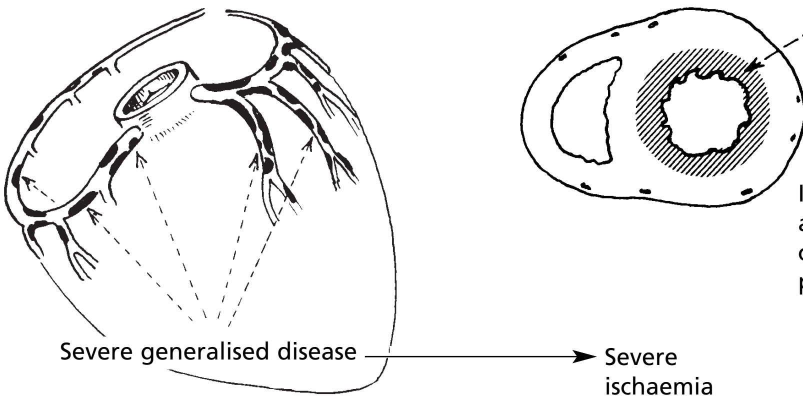
COMPLETE OCCLUSION is usually accompanied by myocardial infarction.

COMPLETE OCCLUSION may be accompanied by only minor damage.

MYOCARDIAL INFARCTION

SUBENDOCARDIAL INFARCTION

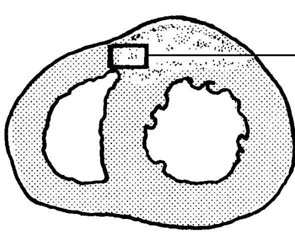
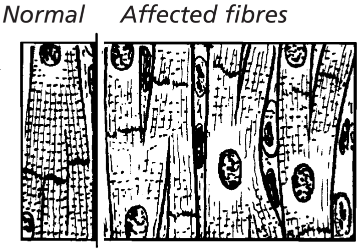
This type occurs round the circumference of the left ventricle under the endocardium in cases of severe stenosis of all the coronary arteries and is often due to hypotension. The coronaries are usually not thrombosed.



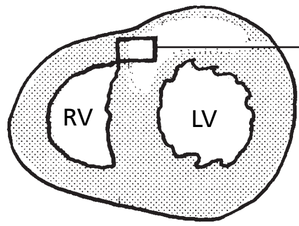
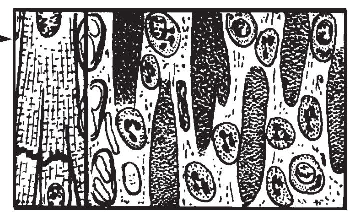
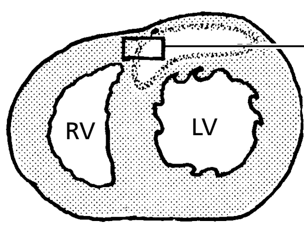
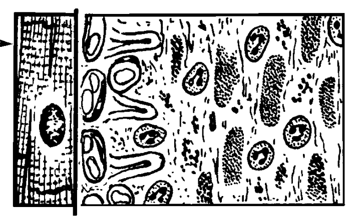
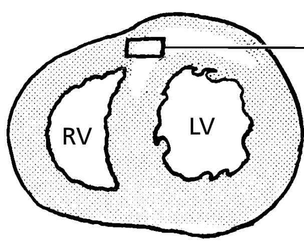
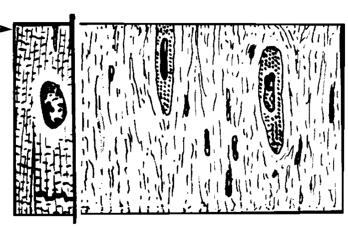
Microscopic focal infarction is necrosis of single or small groups of muscle fibres at the margins of areas of myocardium previously damaged by ischaemia and is a component of progressive chronic ischaemia.

The **time scale** of the pathological changes following acute infarction is illustrated.

1. During the first 24 hours changes are minimal.

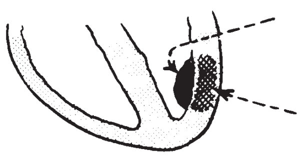
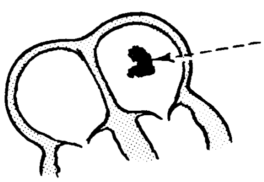
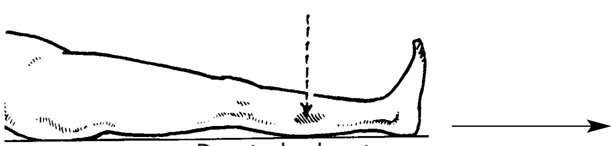
Time			
0–24 hrs	Minimal change	Slight blotchiness (congestion and pallor) of infarcted area 	Slight separation of fibres; slight increase of leucocytes between fibres; slight disturbance of cell cytoplasm *Normal* *Affected fibres* 

MYOCARDIAL INFARCTION

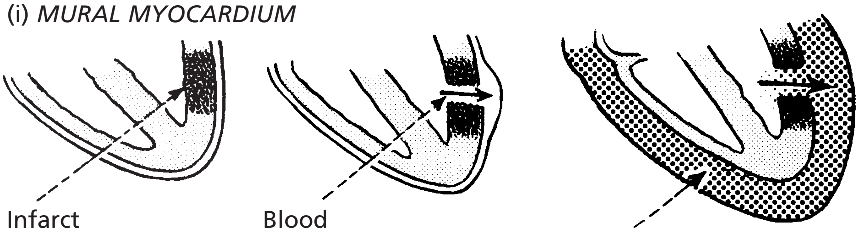
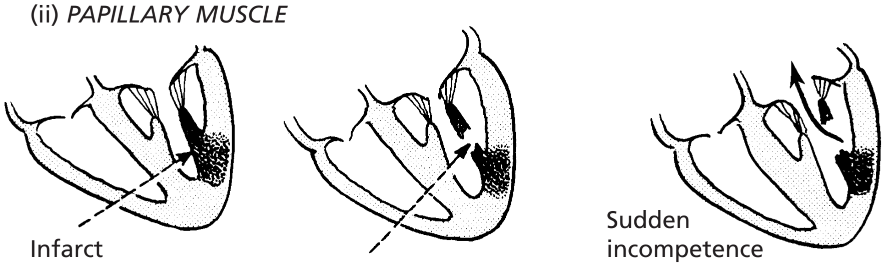
Time			
24 hrs –3 days	Definite changes in dead muscle	Dead muscle, paler yellow *Note:* Usually a thin layer of healthy muscle under the endocardium 	Dead muscle fibres have lost striations and nuclei; cytoplasm glassy pink (H & E staining); capillary congestion at margin; neutrophils and macrophages increasing in number 
3–10 days	Healing (organisation) commencing	Margin of congestion (redness) appearing round dead muscle and resorption of muscle becoming visible at the edges 	Muscle fibres splitting up and being resorbed; granulation tissue at edges; neutrophils still present 
Weeks – months	Scar tissue – healing complete	White fibrous tissue 	Scar tissue – may be occasional surviving muscle fibres embedded 

These changes represent the uncomplicated continuous process of healing. However, complications are frequent, producing serious, often fatal, effects.

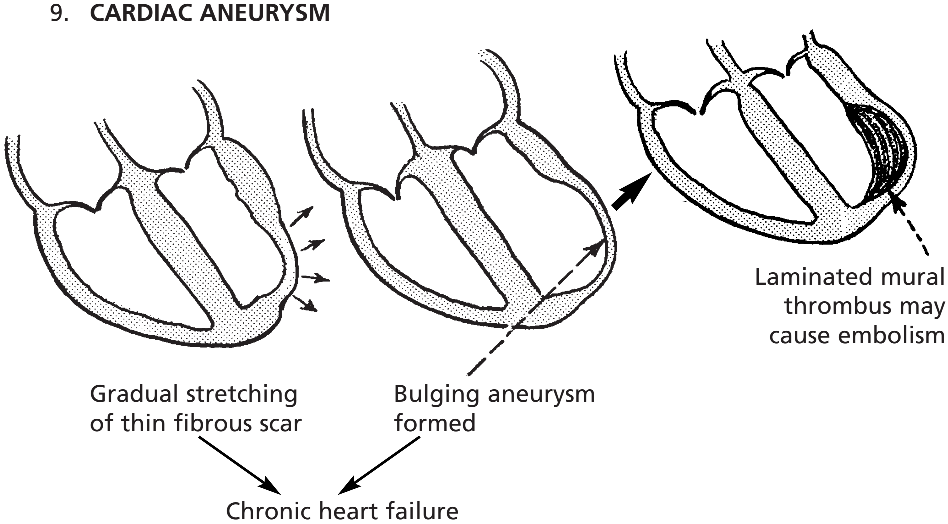
MYOCARDIAL INFARCTION

Time	**COMPLICATIONS**
Minutes, hours	1. **ARRHYTHMIAS** (a) *Ventricular fibrillation*, i.e. cardiac arrest (especially liable at onset of infarction and during first few days). (b) *Heart block of impulse* conduction in Bundle of His and/or its branches – usually causes slowing of ventricular rhythm or upsets the balance of ventricular contraction. 2. **CARDIAC FAILURE** 3. **CARDIOGENIC SHOCK** Associated with large infarcts.
Days	4. **THROMBOTIC COMPLICATIONS** (a) **MURAL THROMBOSIS**  Thrombus may form on endocardium over site of infarction: potential EMBOLISM to Brain Intestine Kidney Lower limbs (b) **ATRIAL THROMBOSIS**  Thrombus may form in atrial appendages – especially if atrial rhythm is disturbed (c) **LEG VEIN THROMBOSIS**  Due to bed rest and venous stasis → **Pulmonary embolism** may be FATAL

MYOCARDIAL INFARCTION

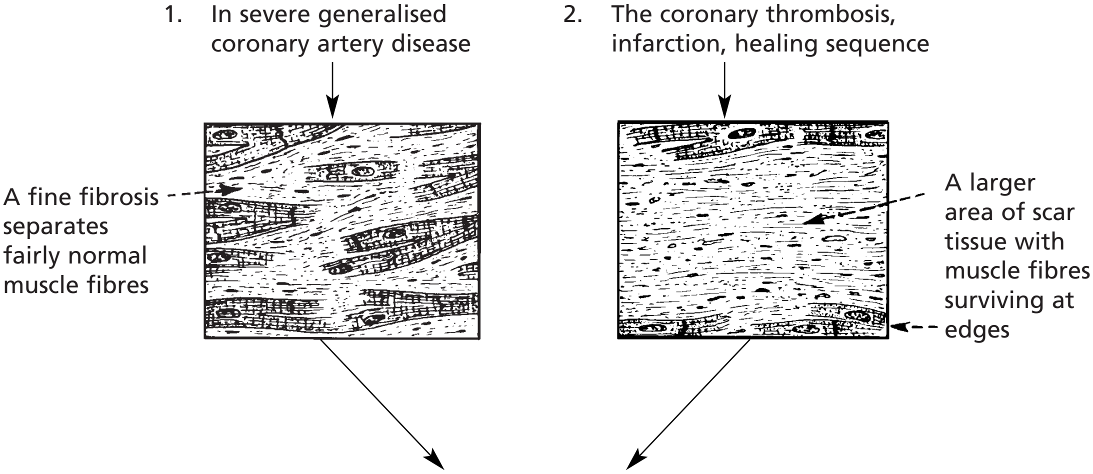
Time	**COMPLICATIONS *(continued)***
3–14 days	5. **RUPTURE OF HEART** Potentiated by: (a) infarction of whole wall thickness (b) unusual increased neutrophil activity before organisation is established → softening of dead muscle (myomalacia cordis). **Sites affected and results** (i) *MURAL MYOCARDIUM*  (ii) *PAPILLARY MUSCLE*  (iii) *INTERVENTRICULAR SEPTUM* 

MYOCARDIAL INFARCTION

Time	**COMPLICATIONS** ***(continued)***
3–14 days	6. **ACUTE PERICARDITIS**
Weeks	7. **CHRONIC HEART FAILURE** At the stage of fibrosis, chronic heart failure may supervene (+ ANGINA PECTORIS). 8. **DRESSLER'S SYNDROME** An auto-immune disorder with pericarditis and pleurisy, related to the release of antigens from damaged heart muscle.
Months	9. **CARDIAC ANEURYSM** 
At any time	10. **RECURRENCE OF INFARCTION** Due to further thrombotic occlusion of a coronary arterial branch.

CHRONIC ISCHAEMIC HEART DISEASE

With chronic ischaemia there is replacement of the myocardial fibres by fibrous tissue which is laid down in two main ways depending on whether the coronary insufficiency is due to severe generalised stenosis or is the result of local infarction following thrombosis.



However, in many cases both mechanisms are present and lesions merge.

Myocardial fibrosis tends to be progressive, reflecting the progression of the atheromatous narrowing of the arteries.

Myocardial hypertrophy from any cause is an important contributory factor in many cases.

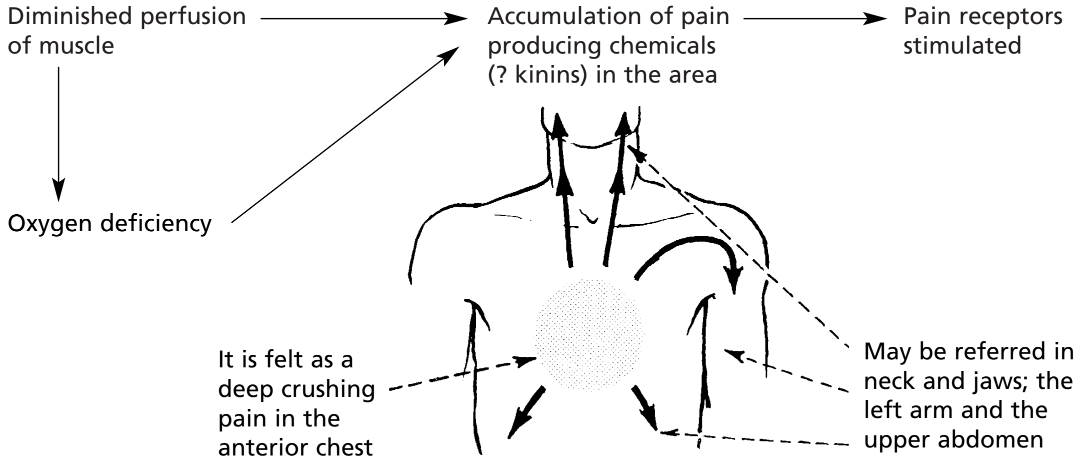
Greater muscle mass → Greater blood supply required → Greater susceptibility to ischaemic damage

Thus hypertension, which causes left ventricular hypertrophy, is an important background factor.

ISCHAEMIC HEART DISEASE

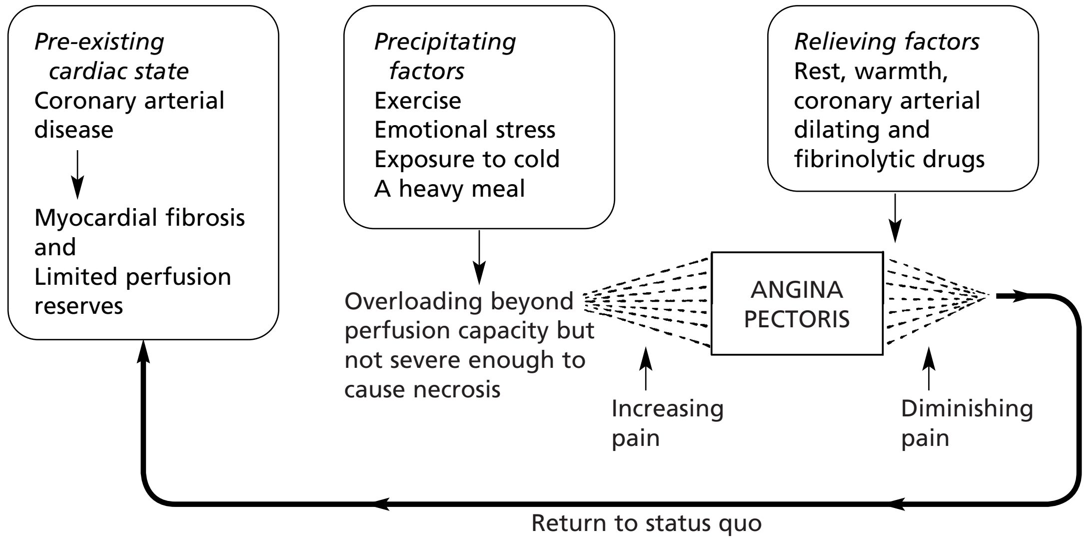
CLINICAL, LABORATORY and ELECTROCARDIOGRAPH (ECG) EFFECTS

Cardiac Pain is caused by muscle ischaemia as follows:



It occurs in 3 main circumstances:

1. **In acute infarction** – especially in the early phases before necrosis is complete. It is usually a continuous pain – not relieved by rest.
2. **In chronic myocardial ischaemia without infarction,** e.g. ANGINA PECTORIS – episodes of cardiac pain brought on by temporary ischaemia.



3. *Note:* The term Crescendo or Unstable Angina refers to rapidly increasing anginal pain over a period of a few days without treatment, usually leading to myocardial infarction. It is due to developing thrombus or plaque rupture.

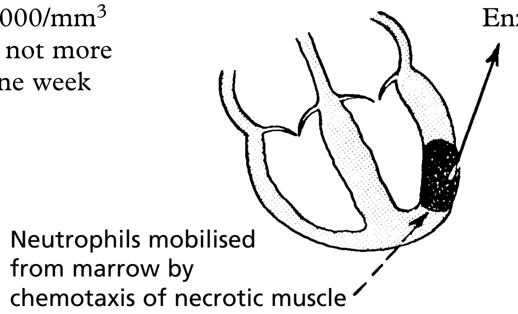
ISCHAEMIC HEART DISEASE

CLINICAL, LABORATORY and ECG EFFECTS *(continued)*

The blood in myocardial infarction

Leucocytosis

12–15 000/mm^3 lasting not more than one week



Enzyme changes

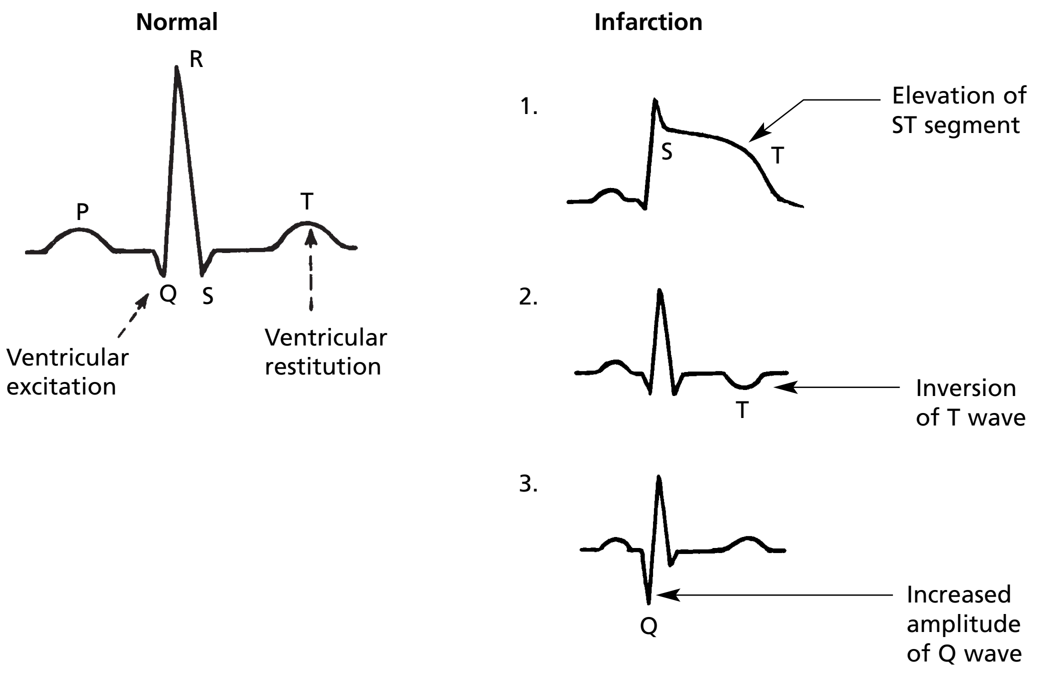
Enzymes liberated from necrotic muscle. Two commonly used in diagnosis:

1. Troponin, within 12 hours of onset.
2. Myocardial creatine kinase (CKMB) is specific for cardiac muscle. Peak in 24 hours; falls in 72 hours.

These changes do not occur in angina pectoris since by definition necrosis has not occurred.

The Electrocardiogram (ECG)

The ventricular changes in ischaemia are reflected in the portion of ECG representing ventricular activity, i.e. the QRST complex. During excitation, contraction and restitution, the electrical potentials across the membranes of necrotic muscle fibres are strikingly different from healthy muscle. The ECG changes may be subtle but three common patterns are illustrated.

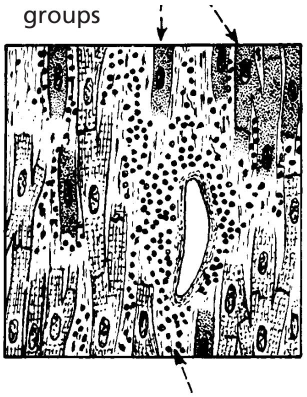


MISCELLANEOUS AFFECTIONS OF THE MYOCARDIUM

MYOCARDITIS

Inflammation of the myocardium is rare. It may be caused by a variety of agents. The process is usually acute and may be generalised, regional or focal; most patients have chest pain but recover: less commonly heart failure develops. Some patients die suddenly. Others go on to develop cardiomyopathy years later.

Agents	Special features	Basic pathology
Viruses e.g. Coxsackie B group and influenza virus	Usually generalised: interstitial inflammation the main feature	Muscle fibre damage – necrosis and lysis of individual or small groups
Bacteria e.g. Lyme disease – *Borrelia burgdorferi*		
Toxins (incl. chemicals) Classic example – diphtheria toxin circulating in blood. Also in other severe infections, e.g. typhoid, pneumonia	Usually generalised: muscle damage the main feature	
Immunological E.g. rheumatic fever – myocarditis is an important component of the disease (see p.214 for details of special features).		Interstitial oedema and inflammatory cellular infiltrate

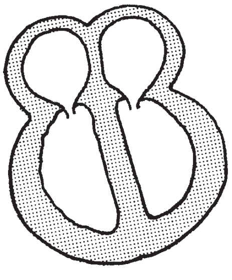


CARDIOMYOPATHY

This term refers to diseases of cardiac muscle when ischaemia, hypertension, valvular disease and inflammation have been excluded. Genetic influences are important.

3 main forms are recognised:

1. **Dilated (congestive) Cardiomyopathy**



This is an uncommon condition which is familial in a minority of cases often due to mutations affecting cytoskeletal proteins. Patients present clinically with unexplained heart failure usually between the ages of 30 and 60 years.

Other causes include myocarditis, alcohol and pregnancy associated.

MISCELLANEOUS AFFECTIONS OF THE MYOCARDIUM

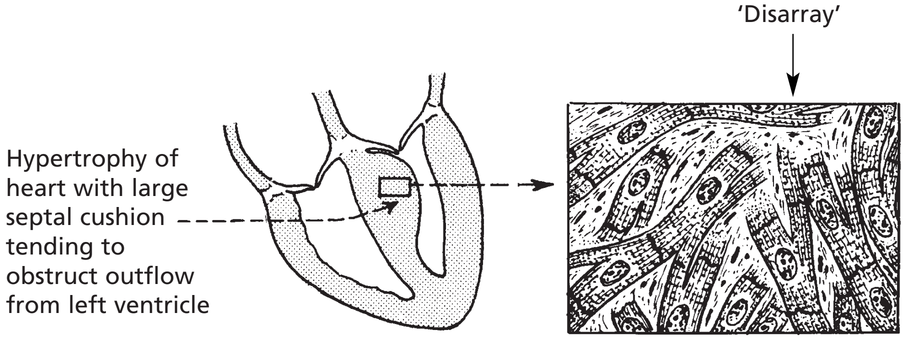
CARDIOMYOPATHY *(continued)*

2a. **Hypertrophic Cardiomyopathy**

This can occur at any age, but young adults are often affected. There is often a family history presenting usually as an autosomal dominant pattern. Several genes encoding contractile protein may be involved, e.g. β-myosin heavy chain.

The effects include: sudden death, often following exercise, arrhythmias and cardiac failure.

Muscle hypertrophy without dilatation occurs. There is disproportionate thickening of the interventricular septum. Histologically the enlarged muscle fibres are arranged irregularly.



2b. **Restrictive Cardiomyopathy**

In this form the myocardium does not relax properly in diastole; this restricts ventricular filling and **cardiac output is reduced.**

A similar problem is seen in **Endomyocardial Fibrosis** – a disease of childhood seen mainly in Africa.

Other myocardial disorders include:

(i) Amyloidosis (p.24).
(ii) Haemochromatosis (p.356).
(iii) Drugs, e.g. alcohol, adriamycin, cocaine.

RHEUMATIC FEVER

In rheumatic fever (acute rheumatism), a disease of children and young adults, inflammation affects the connective tissues at many sites, of which the **heart** is the most important. The incidence in Western countries has fallen dramatically, but it is common in parts of Africa and Asia.

Aetiology
There is a strong association with streptococcal sore throat. Streptococcus is important because it shares antigens with human tissues, particularly heart muscle.

Mechanism

Throat infection due to β-haemolytic streptococcus (Group A) → IMMUNE RESPONSE → Cell mediated and ANTIBODIES to STREPTOCOCCAL ANTIGENS → CROSS-REACTION with CARDIAC and connective tissues of SUSCEPTIBLE individuals

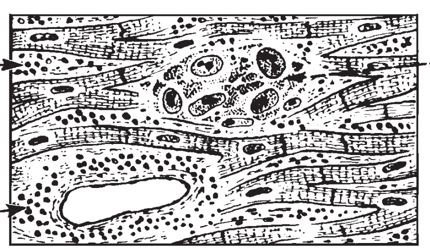
In addition to the cardiac damage, the disease is manifest in the following ways:

1. **General manifestations** include:
   Fever with sweating and malaise: raised ESR and C-reactive protein: neutrophil leucocytosis.
2. **Localized inflammation**
   (a) *Joints and adjacent musculofascial tissues* – causing ARTHRITIS with effusion, muscle pains and weakness.
   (b) *Serous membranes* – pericardial and sometimes pleural effusion.
   (c) *Skin* (i) a rash (erythema marginatum).
   (ii) small subcutaneous palpable nodules over bony prominences subject to pressure.
   (d) *Central nervous system* – chorea (involuntary spasmodic muscular movements).

CARDIAC MANIFESTATIONS

The inflammation is widespread throughout the heart (PANCARDITIS) – affecting the pericardium, myocardium and endocardium.

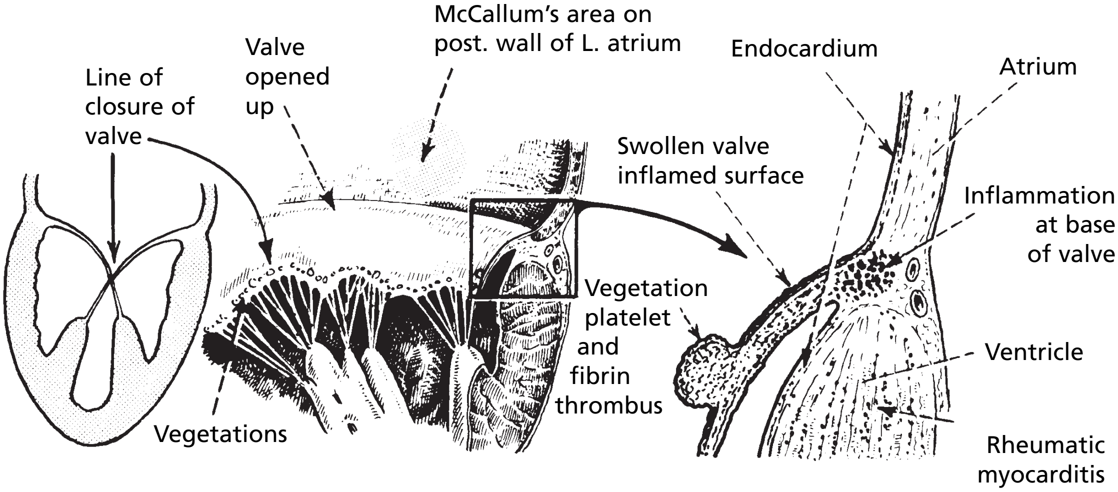
1. **Pericarditis** occurs during the acute phase of the illness and is an important cause of pericardial effusion.
2. **Myocarditis** is common during the acute phase and is usually mild: it is rarely severe enough to cause cardiac failure. The histological picture is striking and the presence of the Aschoff body is characteristic.



RHEUMATIC FEVER

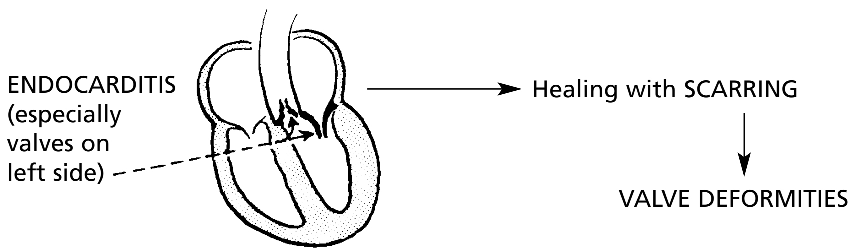
CARDIAC MANIFESTATIONS *(continued)*

3. **Endocarditis.** Although there is a widespread histological inflammation, gross changes are seen usually on the endocardial sites subject to the greatest pressures and traumas, i.e. in the left side of the heart at the points of valve closure and at any sites of jet effect in the blood flow. The inflammation is complicated by ulceration of the valve surface followed by platelet and fibrin thrombosis in the form of small 'vegetations'.



Progression of the disease

In most cases the acute phase passes off and is followed by healing with various degrees of scarring. In a significant number of cases, no florid acute phase is noticed, and in a small number, a low grade chronic inflammation is present for long periods. Repeated episodes lead to chronic valvular heart disease in about 50% of patients.



VALVULAR HEART DISEASE

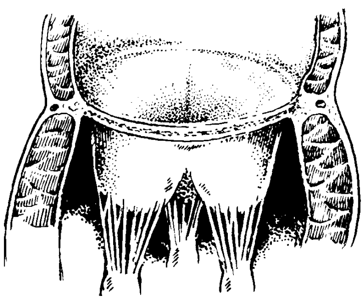
The main causes are RHEUMATIC FEVER, degenerative changes including DYSTROPHIC CALCIFICATION and congenital heart disease. Inherited deficiencies of the ground substance of the valve are rare causes. Nowadays, with the advent of powerful antibiotics, the late effects of healed infective endocarditis are assuming greater importance.

The MITRAL and AORTIC valves, subjected to much greater pressures, are more susceptible to damage than the tricuspid and pulmonary valves. *Rheumatic mitral disease* has been very common in the past and is still seen in middle aged or older patients, but with the decline in rheumatic fever and the increasing age of the population, *calcific aortic disease* is now commoner.

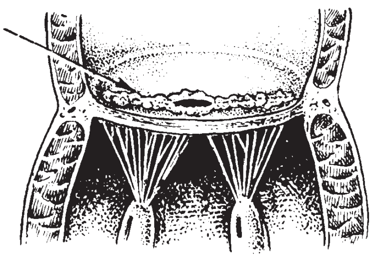
MITRAL DISEASE

Mitral valve stenosis is most commonly the result of post-inflammatory scarring as a consequence of rheumatic fever.

Normal valve
Note thin delicate curtains and chordae tendinae.



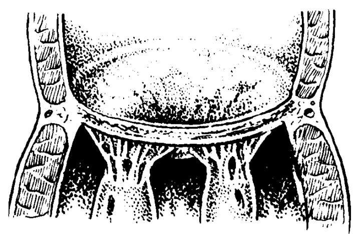
Stenosis
Simple adherence of curtains: a diaphragm formed (balloon valvuloplasty or valvotomy may be possible).



OR

Adherence and distortion, thickening, shortening, calcification of valve curtains and chordae resulting in 'funnel' stenosis.

(Whole valve replacement required.)

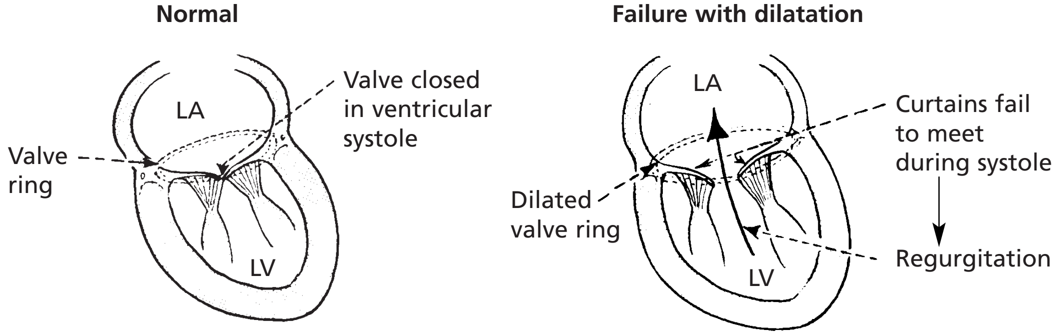


MITRAL VALVE DISEASE

Mitral disease *(continued)*

Mitral value incompetence has many causes:

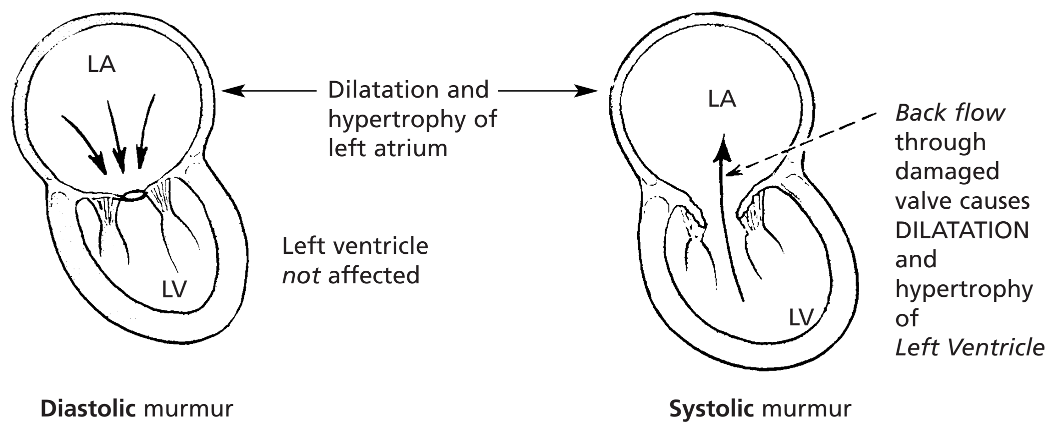
1. Post inflammatory scarring, i.e. rheumatic fever.
2. In cases of left ventricular failure when severe dilatation occurs.



3. Necrosis with rupture of papillary muscle in acute myocardial infarction.
4. It may result from myxoid degeneration of the valve – the 'floppy valve syndrome'. This most commonly affects young women. The enlarged 'floppy' valve prolapses into the left atrium during systole.
5. Infective endocarditis (see p.222).

The mechanical effects of mitral disease

Chronic stenosis – pure ***Chronic incompetence – pure***



In rheumatic heart disease combined stenosis and incompetence is often seen.

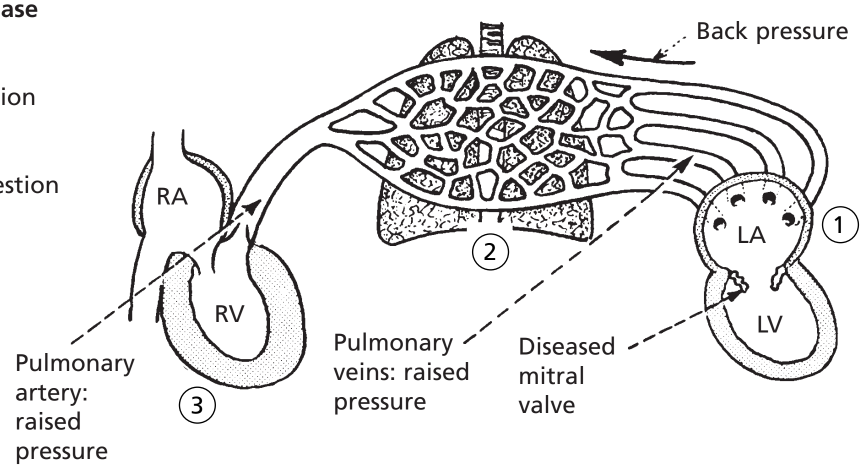
MITRAL VALVE DISEASE

Mitral disease *(continued)*

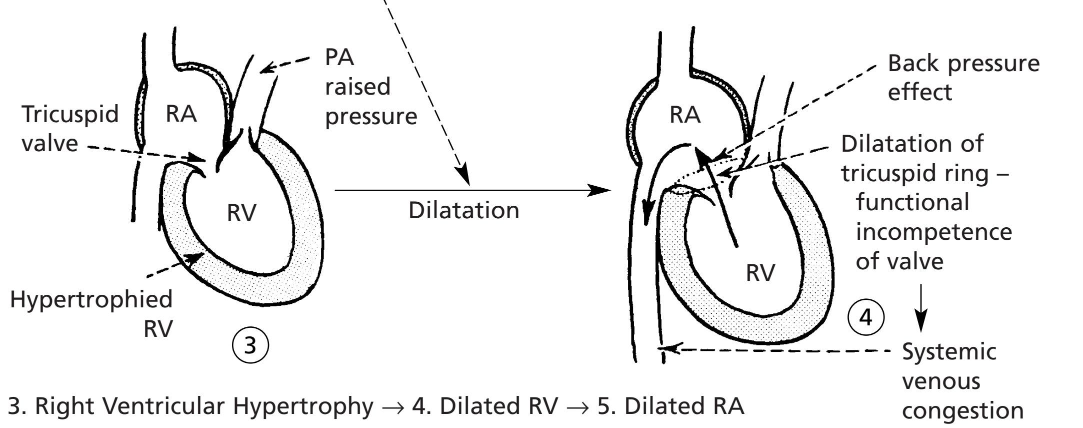
In mitral disease, the back pressure in the left atrium is transmitted to the pulmonary veins and by raising pulmonary arterial pressure causes effects on the right side of the heart.

(a) **Compensated phase**

1. Left atrial dilatation
↓
2. Pulmonary congestion
↓
3. Right ventricular hypertrophy



(b) **Congestive cardiac failure**



3. Right Ventricular Hypertrophy → 4. Dilated RV → 5. Dilated RA

In the acute types of mitral incompetence, the sudden change in the intracardiac haemodynamics very seriously aggravates the heart failure already present due to the primary disease.

Complications of chronic mitral disease

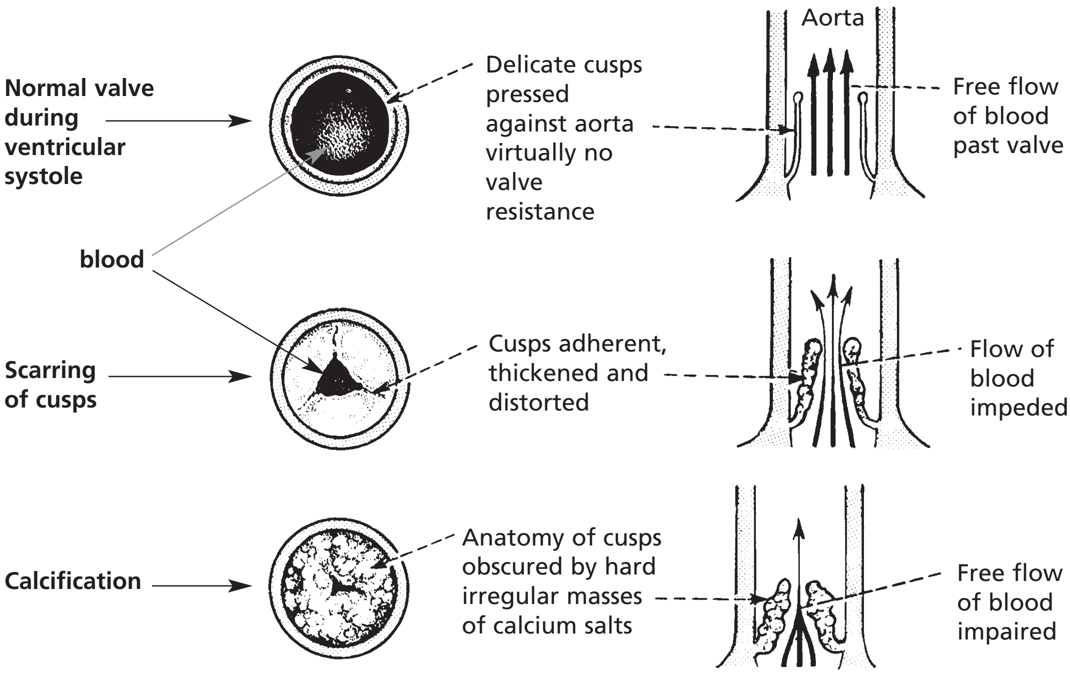
1. Atrial fibrillation is common.
   Fibrillation → Thrombosis in atrial appendage → Systemic embolism
2. Infective endocarditis.

AORTIC VALVE DISEASE

STENOSIS

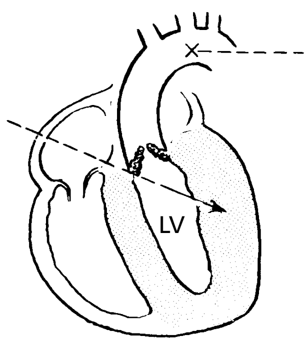
The main causes are SCARRING and CALCIFICATION occurring in a CONGENITALLY ABNORMAL VALVE (usually bicuspid) or an anatomically normal valve previously damaged by rheumatic fever or endocarditis (bacterial).

Changes in the valve



Effects

The main effect is HYPERTROPHY of the left ventricle to overcome the valve resistance,
e.g. 600 g
(normal – 300 g)



Ejection systolic murmur

Low pulse pressure may reduce flow in the coronary arteries. The hypertrophied muscle is therefore susceptible to ischaemic damage.

The heart often remains in this ‘compensated’ state for years but eventually failure develops with dilatation.

SUDDEN DEATH (without pre-existing signs of failure) is a definite risk at any time, but particularly during exercise.

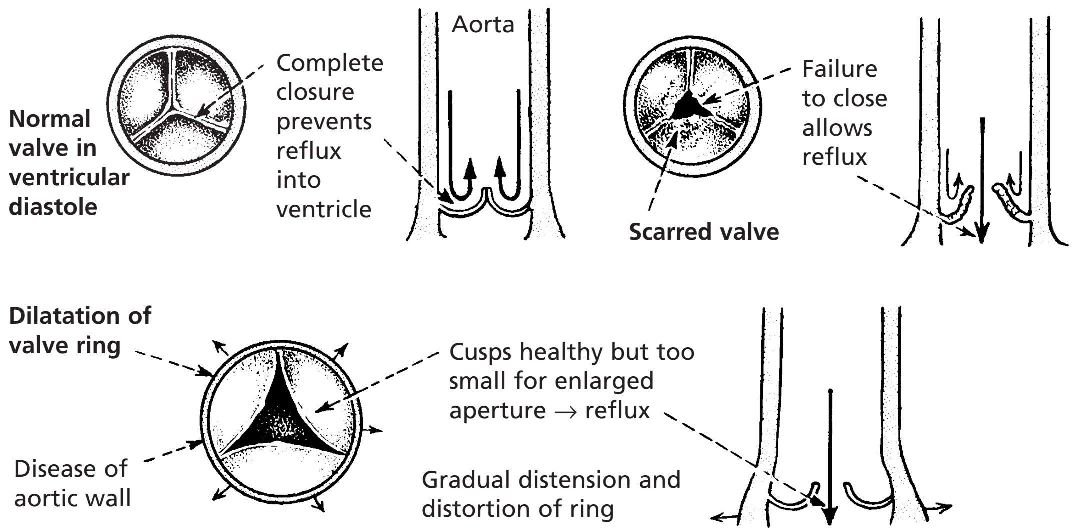
In adults, severe aortic stenosis usually requires valve replacement.

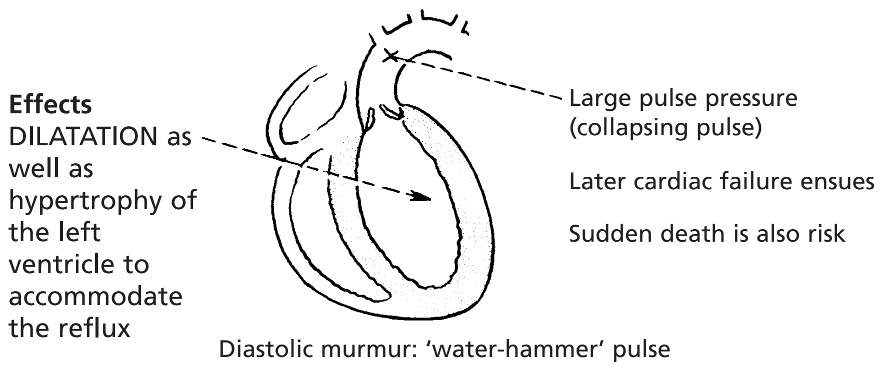
AORTIC VALVE DISEASE

INCOMPETENCE

The main causes are scarring of the cusps due to rheumatic fever or infective endocarditis: less commonly dilatation of the valve ring due to disease (e.g. in ankylosing spondylitis: Marfan's syndrome) or degeneration in old age.

Changes in the valve





Aortic stenosis and incompetence often exist together and the effects are compounded.

TRICUSPID AND PULMONARY VALVES

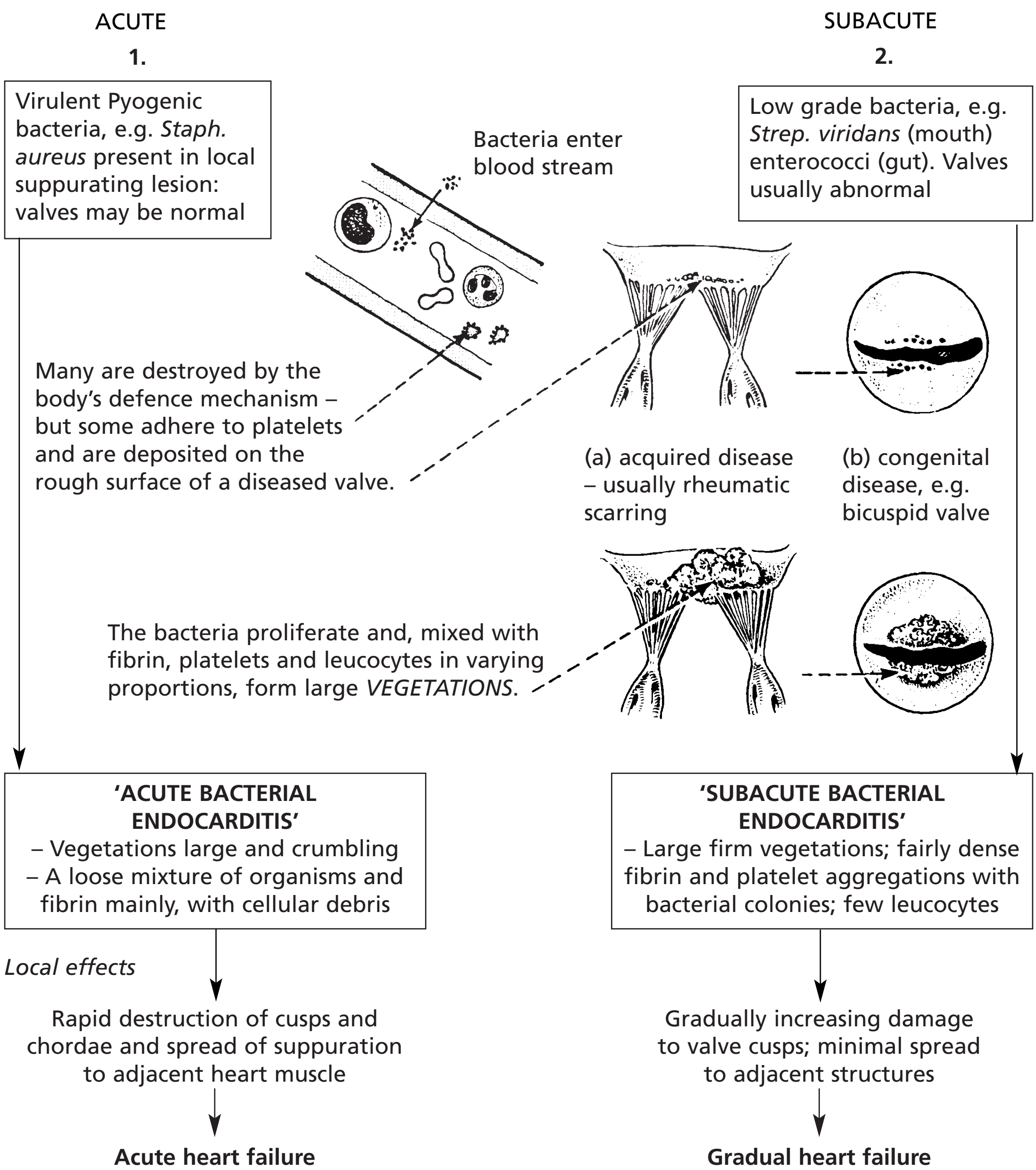
Diseases of these valves are not common. However functional tricuspid incompetence due to severe cardiac dilatation is an important end stage in progressive cardiac failure.

Progressive failure → Dilatation → TRICUSPID INCOMPETENCE → Right atrial failure → Severe systemic venous congestion (congestive cardiac failure)

INFECTIVE ENDOCARDITIS

In this disease, there is colonization or invasion of the heart valves by micro-organisms leading to the formation of friable vegetations. In many cases the values have been previously damaged, e.g. by rheumatic fever. In other cases, normal values may be affected by particularly virulent organisms, e.g. intravenous drug users.

Endocarditis has traditionally been classified into acute and subacute forms.



INFECTIVE ENDOCARDITIS

In addition to the local effects, there may be systemic complications:

1) Embolism
   – embolic infarction and pyaemic abscesses may occur in the brain or kidneys
   – glomerulonephritis due to antigen – antibody complexes becoming trapped in the kidney
2) Pyrexia
3) Leucocytosis.

Valves in immunocompromised patients may be colonised by opportunistic organisms, e.g. fungi.

Cardiac prostheses and catheter lines act as a focus for bacterial growth and infective endocarditis is a serious complication.

CARDIAC ARRHYTHMIAS

CARDIAC ARRHYTHMIAS and DISEASES of the CONDUCTING SYSTEM

Of the wide variety of cardiac arrhythmias which have now been studied in detail using the electrocardiograph, the majority are due to (A) functional disturbances of the intrinsic excitability of the cardiac muscle at various sites or of the cardiac neurohumoral controls; only a minority are due to (B) organic disease of the conducting system itself.

A Important disorders of cardiac muscle excitability

1. **Atrial fibrillation**
   This is a common condition in which there is irregular, rapid and ineffective atrial contraction.

Predisposing conditions
Ischaemic heart disease
Rheumatic heart disease
Hypertension
Thyrotoxicosis

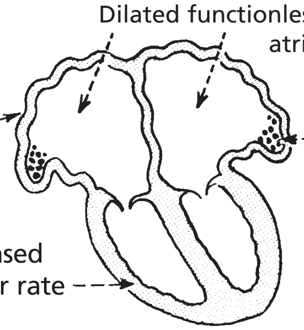
} Atrial dilatation (± atrial muscle hypertrophy) → Atrial fibrillation

(Increased susceptibility to 'circus' rhythm)

There are two main effects:

(a) *Contribution to cardiac failure*

(b) *Intra-atrial thrombosis and embolism*



2. **Ventricular paroxysmal tachycardia and fibrillation**
   These usually occur in association with ischaemic heart disease. In fibrillation, a form of cardiac 'arrest', cardiac function ceases.

CARDIAC ARRHYTHMIAS

Cardiac arrhythmias *(continued)*

B Diseases of the conducting system

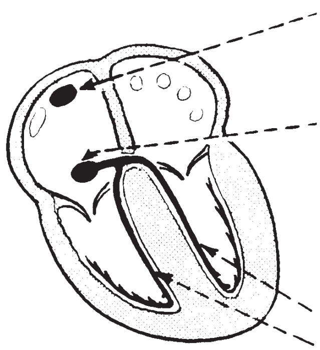
This is usually due to disease in the adjacent heart tissue. The heart rate is slow.

Associated conditions

Cardiac ischaemia — Acute infarction / Fibrosis } — are the most common and important

Others are – myocarditis, calcification around the valve rings and drugs, e.g. digitalis, propranolol.

Sites of disorder — **Effects**



SA node – Sinus bradycardia
Paroxysmal supraventricular tachycardia

AV node and Bundle of His —
Heart block
1st degree: only mild delay in conduction
∴ no effect on ventricular rate
2nd degree: moderate delay, missed ventricular beats
3rd degree: complete block, idioventricular rhythm established, 25–50 per min

Left and right bundles — *Bundle branch block*
Causes loss of efficiency of ventricular contraction

The 3 important components of arrhythmias are:
Tachycardia, bradycardia and irregularity.
The effect of any arrhythmia on cardiac function depends essentially on its effect on ventricular output.

Tachycardia
pulse rate over 160/min → Diastolic time too short to allow adequate ventricular filling; also impairment of coronary flow → Low cardiac output → Failure

Tachycardia ↓ Seriously aggravated by **Irregularity** ↑ Bradycardia

Bradycardia
– pulse rate less than 60/min → Low cardiac output

CONGENITAL HEART DISEASE

Developmental abnormalities of the heart are relatively common; clinically significant defects occur in 7–11 per 1000 live births and the rate is significantly higher in stillbirths. The severity varies from minor aberrations to complex distortions incompatible with life. Many patients now live normal lives after cardiac surgery.

Aetiology
This is often obscure. Hereditary factors are of limited importance, Down syndrome often causes septal defects. Possible environmental factors are complex and numerous.

Examples include: virus infection, e.g. rubella; teratogen, e.g. thalidomide (historically); altitude at birth (patent ductus arteriosus is commoner at high altitudes).

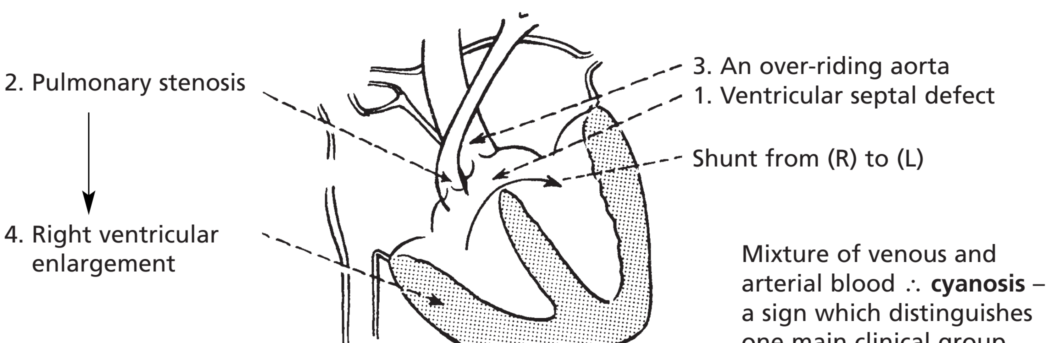
The initial damage which is sustained during the first trimester of pregnancy is modified by later fetal and postnatal growth and development.

Single anatomical abnormalities occur, but often there are multiple defects which are associated in groups of which the more common are given specific names.

Abnormal development occurs:

1. At the emergence of the great vessels
   ↓
   Stenoses cause impedence to blood flow
2. During formation of the septa between right and left sides and following failure of closure, e.g. ductus and foramen ovale.
   ↓
   Abnormal apertures allow shunting of blood

Fallot's tetralogy is an example of congenital heart disease in which there is cyanosis. There are 4 components:



Often complications – pulmonary hypertension, increased blood volume, polycythaemia, and infective endocarditis – increase the disability.

Surgical repair is the ideal treatment.

DISEASES OF THE PERICARDIUM

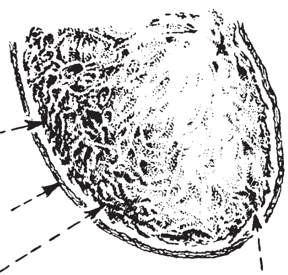
PERICARDITIS

Pericarditis is a complication of diseases of the heart or adjacent structures or of generalised disorders. In some cases no cause can be found.

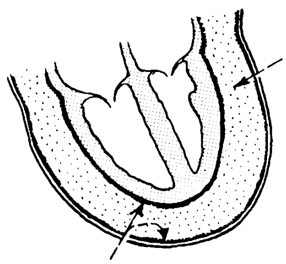
Acute pericarditis may be:

1. Fibrinous - this is the commonest form and is seen in acute MI and anaemia
2. Serous - e.g. in rheumatic fever, scleroderma, SLE
3. Purulent - due to invasion of the pericardial space by infectious organisms
4. Haemorrhagic - e.g. with trauma or tumour.

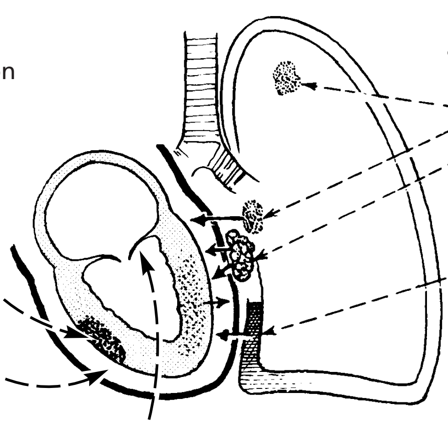
Fibrinous pericarditis



Pericarditis with effusion



Diseases which may lead to pericarditis

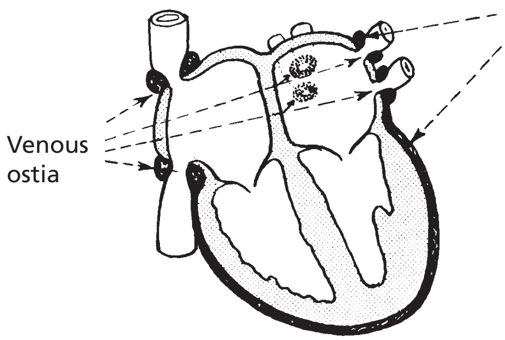


(c) *Generalised disorders*

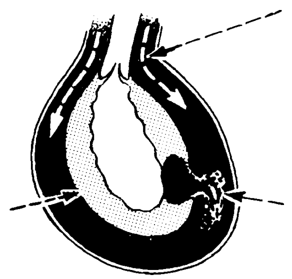
(i) uraemia
(ii) connective tissue diseases, e.g. SLE, rheumatoid disease

DISEASES OF THE PERICARDIUM

CHRONIC PERICARDITIS may be due to tuberculosis, viral infection or rheumatoid arthritis; sometimes the cause cannot be determined. The basic changes are organisation and calcification. In extreme cases, cardiac function is impaired.

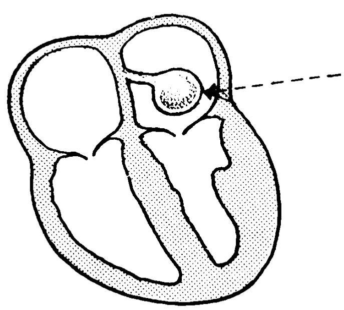


PERICARDIAL HAEMORRHAGE occurs most commonly as a result of **cardiac rupture** complicating acute infarction. The other main cause is rupture of dissecting **aortic aneurysm** back into the pericardium. The pericardial sac becomes distended with blood (tamponade) and death follows rapidly due to compression of the heart.



CARDIAC TUMOURS

Primary tumours in the heart are very rare. Secondary tumours, especially from the lungs, affecting the pericardium by direct spread and the heart by blood spread are fairly common in advanced malignant disease.



Atrial 'myxoma' is a rare tumour affecting usually the left atrium in which a smooth, pale, soft, rounded mass is attached by a pedicle to the endocardium. It can cause serious effects by occluding the mitral valve opening or by embolisation. Mesothelioma may present primarily in the pericardium.

Rhabdomyomas are occasionally seen in childhood associated with tuberous sclerosis.

DISEASES OF ARTERIES

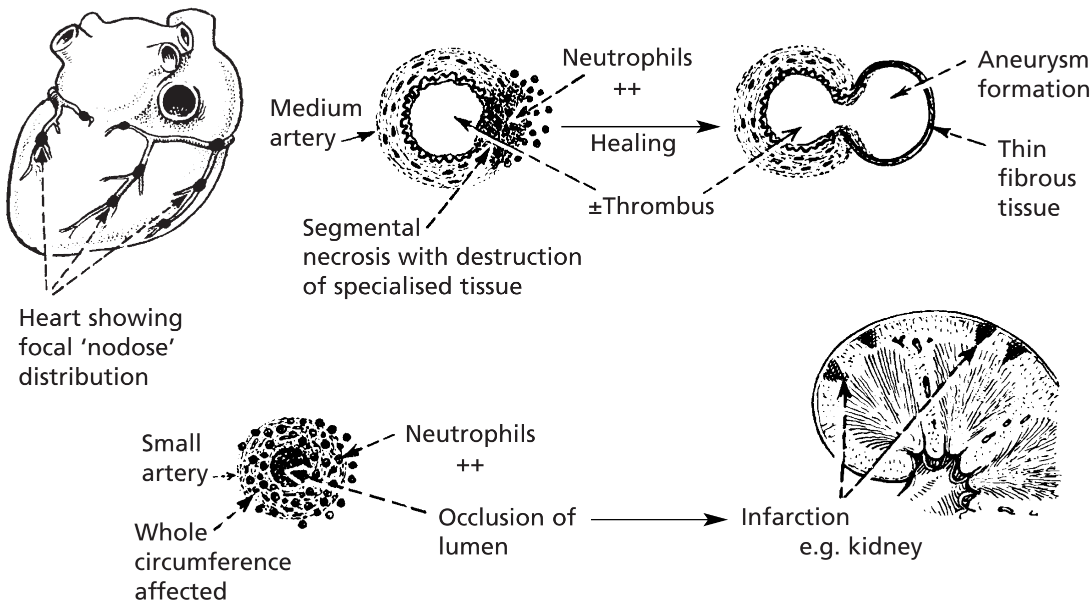
ARTERITIS

The term 'arteritis' refers to a group of conditions with inflammation of the arterial wall, usually due to immune mechanisms. Large, medium or small arteries may be affected.

Polyarteritis nodosa (PAN)

This is a disease affecting the medium and small arteries and arterioles. In the acute phase, there are signs of generalised illness with fever, etc., but the disease often becomes chronic and relapsing.

Typically there is a focal necrosis of the arterial wall.



Any artery may be affected, but damage to the HEART, KIDNEYS, BRAIN and GUT is particularly important. When the arteries supplying peripheral nerves are affected symptoms of 'neuritis' may be striking.

In **microscopic polyarteritis**, there is a form of glomerulonephritis due to involvement of afferent arterioles as well as pulmonary capillaritis.

Other forms of arteritis include, for example, *Wegener's granulomatosis* in which destructive lesions of the nasal mucosa, the lungs and the kidneys are seen.

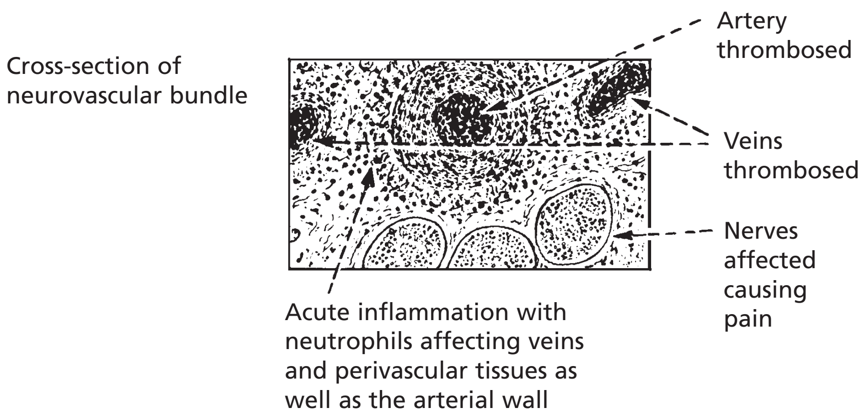
Aetiology PAN appears to be due to antigen: antibody complexes. Hepatitis B infection is the source of antigen in some cases. Anti-neutrophil cytoplasmic antibodies (ANCA) occur in various forms of vasculitis – p-ANCA in microscopic polyarteritis and c-ANCA in Wegener's granulomatosis.

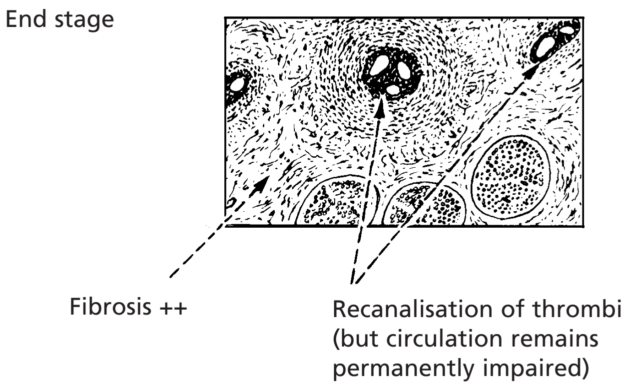
Arteritis may also complicate other conditions (usually the *collagen diseases*, see p.610), e.g. rheumatoid arthritis, systemic lupus erythematosus (SLE).

DISEASES OF ARTERIES

BUERGER'S DISEASE (thromboangiitis obliterans)

In this very painful condition, the inflammation involves the small peripheral arteries of the legs and often the arms. This typically affects young Jewish males (20–40 years) who are **heavy cigarette smokers**.





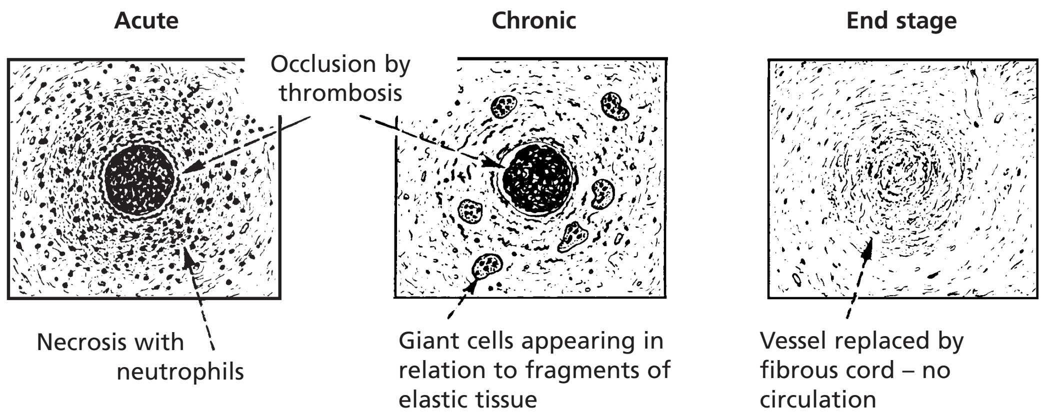
GANGRENE of the toes may follow as more vessels become involved.

DISEASES OF ARTERIES

Temporal arteritis (Giant-cell arteritis/cranial arteritis)
This disease of unknown aetiology affects elderly people (over 65 years). It may cause severe facial pain and headache and may be associated with ocular symptoms and cause blindness. In a significant number of old people, there are no symptoms.

Some cases occur along with polymyalgia rheumatica – a disease in which there are generalised muscle pains and systemic malaise. Commonly, branches of the external carotid arteries are affected, but sometimes other caudal arteries and even the aortic arch may also be involved.

There is inflammation of the vessel wall complicated by thrombosis.



Takayashu's disease
This rare disease, typically affects young females (20–30 years). The patchy arteritis is more severe and affects the aorta and its primary branches, leading to ischaemia of BRAIN (cerebral arteries), EYES (ophthalmic arteries), FACE (carotid arteries), ARMS ('pulseless' disease), HEART (coronary orifices), KIDNEYS (causing HYPERTENSION) in varying combinations.

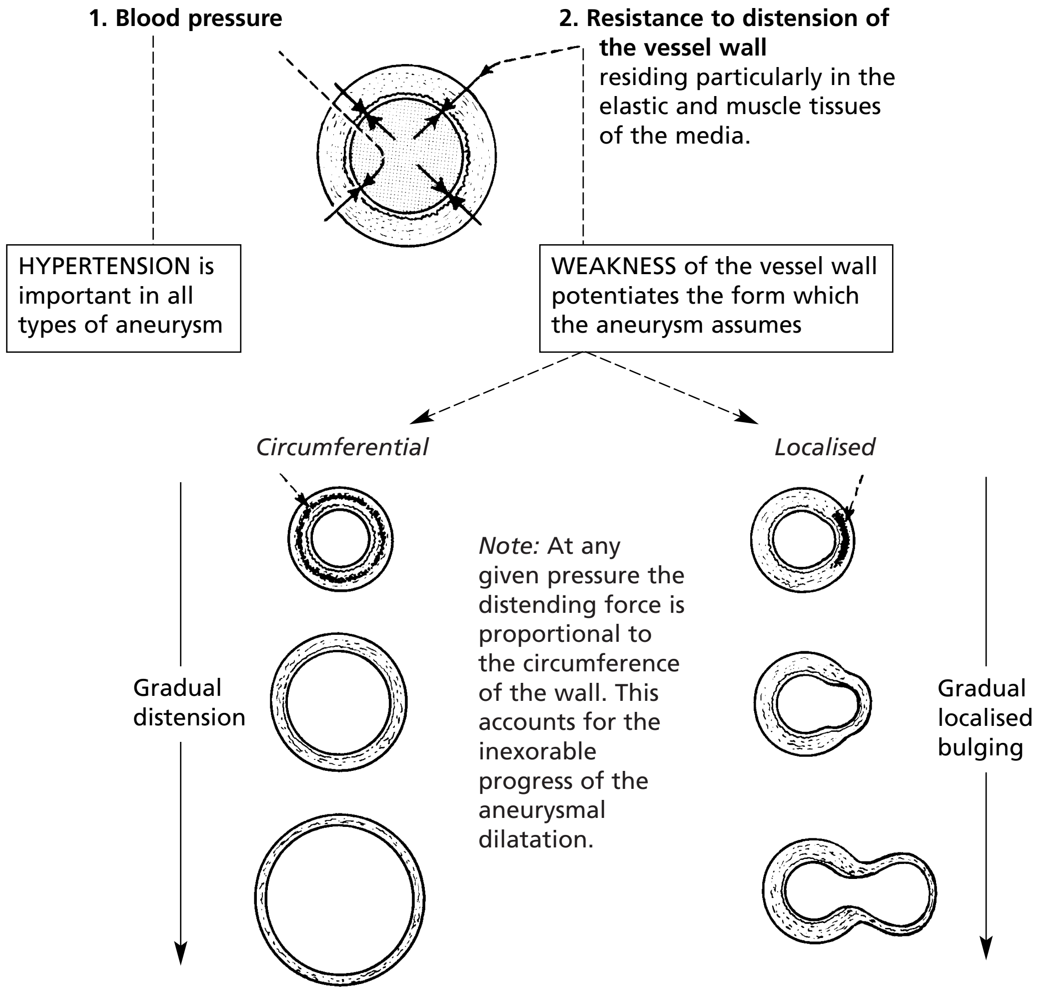
The important vascular changes in diabetes mellitus are described on page 637.

ANEURYSMS

A local enlargement of an artery is called an **aneurysm**. Although localised, it often reflects the presence of more widespread arterial disease.

MECHANISM of FORMATION

The two main forces that maintain the integrity of the shape of an artery are:



Causes

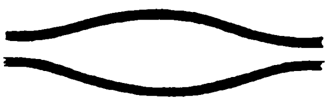
Aneurysms may be due to: acquired diseases of vessel wall (atheroma, arteritis, syphilis (now rare)); congenital weakness (berry aneurysms, pp.233, 539); hypertension; trauma.

ANEURYSMS

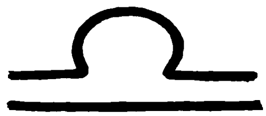
TYPES of ANEURYSM

There are two main varieties:

1. **Fusiform**

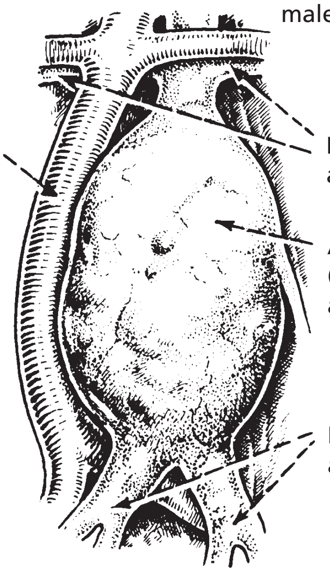


2. **Saccular**



These are well illustrated in the aorta.

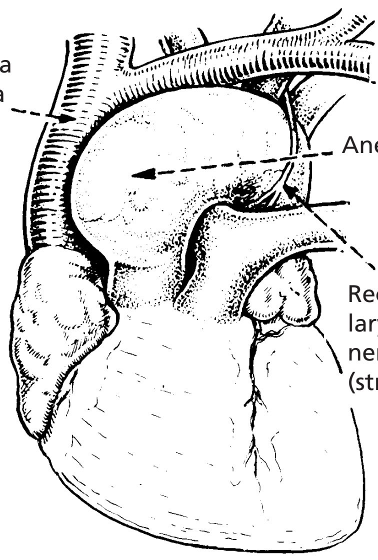
Fusiform aneurysm of abdominal aorta – usually due to atheroma; often below renal arteries and may also affect iliac arteries.



Complications

1. Local pressure effects – usually not serious.
2. Thrombosis with embolism to legs.
3. Rupture with fatal retroperitoneal or intraperitoneal haemorrhage.

Saccular aneurysm of aortic arch – now usually due to atheroma: in the past, syphilis.



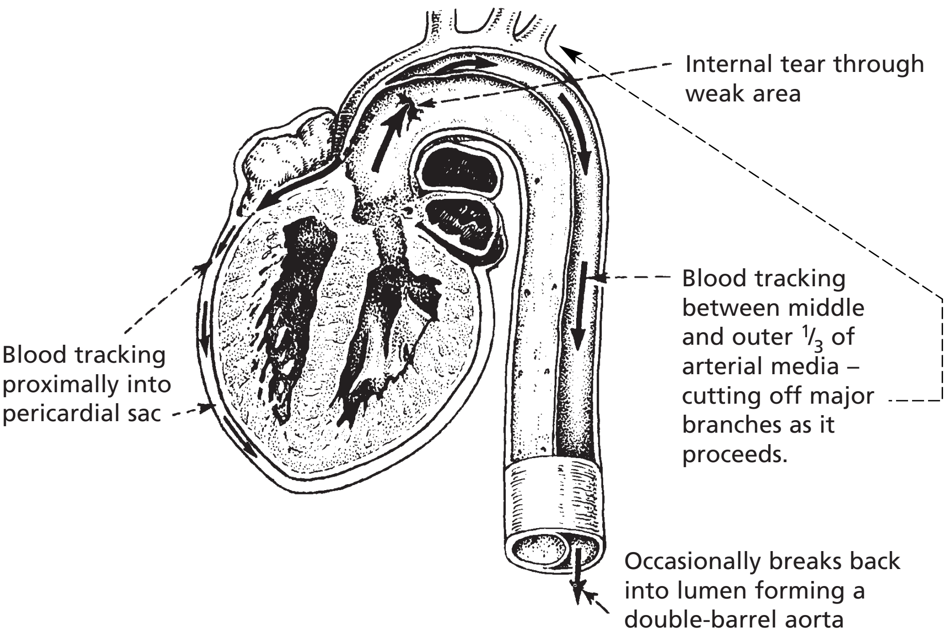
Complications

1. Pressure effects
   (a) on nerves, e.g. recurrent laryngeal nerve paralysis
   (b) on bones e.g. vertebral, sternal or rib erosion
   (c) on neighbouring viscera, e.g. oesophagus, heart, lungs.
2. Fatal haemorrhage.

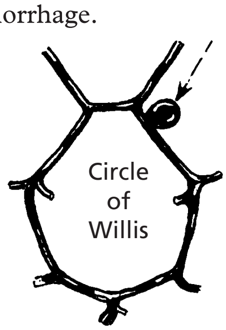
ANEURYSMS

OTHER VARIETIES of ANEURYSM

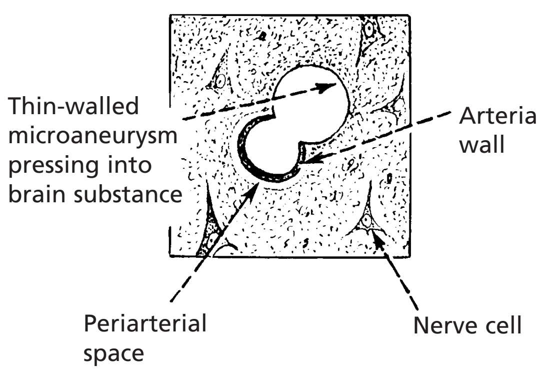
1. **Dissecting aneurysm**
   Classically begins in the arch of aorta.
   Predisposing causes: (a) HYPERTENSION (common)
   (b) Atheroma
   (c) Medial degeneration (rare) seen in Marfan's syndrome due to mutation of the fibrillin gene.



2. **'Berry' aneurysm** occurs in medium-sized vessels at the base of the brain, e.g. on Circle of Willis. Associated with congenital deficiency of arterial media. Rupture causes subarachnoid haemorrhage.



3. **Microaneurysm** – associated with hypertension and affects smaller arteries and arterioles, especially in the brain.



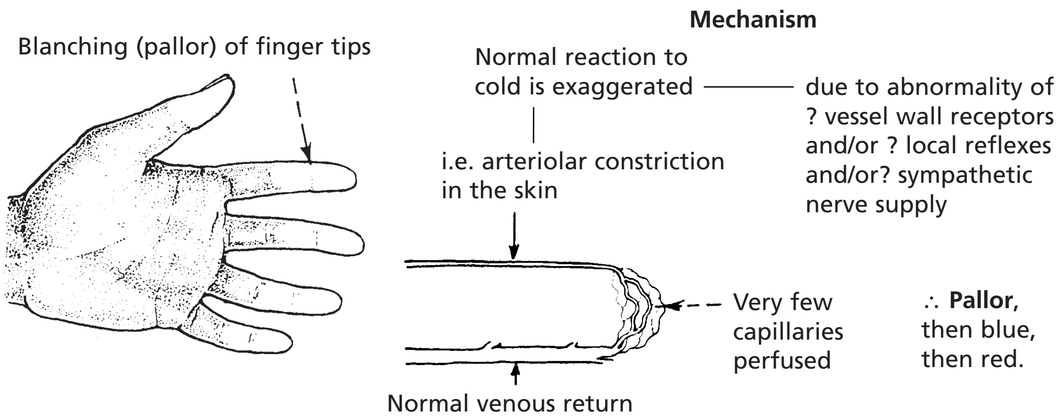
Rupture causes intra-cerebral haemorrhage.

ARTERIAL DISEASES – MISCELLANEOUS

RAYNAUD'S PHENOMENON

There are spasmodic attacks of pallor of the fingers (the toes, ears and nose may also be affected) due to intense constriction of the small arteries and arterioles in response to cold. The cause is not known.

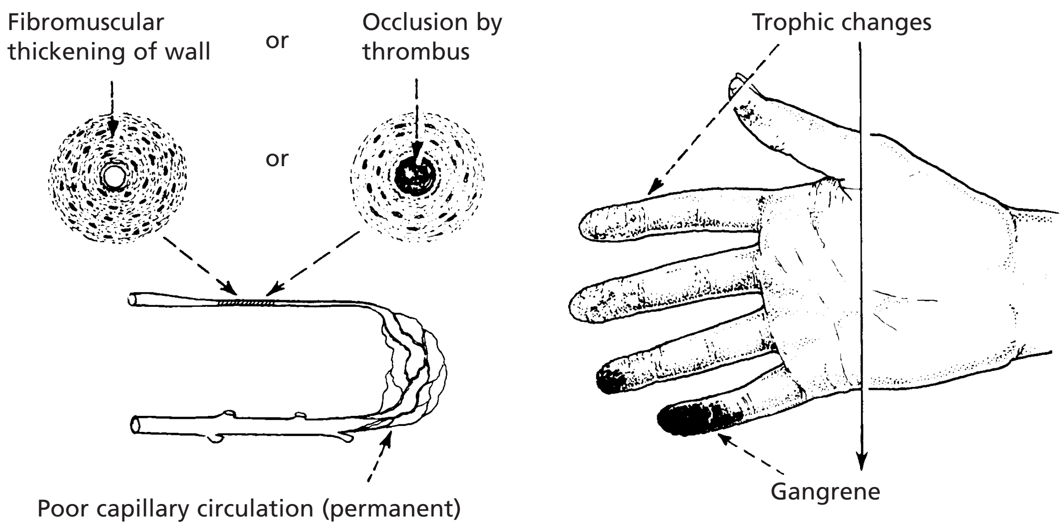
The condition affects 5–10% of young women in temperate climates.



This condition may continue for many years and NO PERMANENT DAMAGE RESULTS.

A **Secondary form** of Raynaud's Phenomenon may occur as a symptom in other conditions. Examples include the 'collagen diseases', systemic sclerosis (see p.610) and systemic lupus erythematosus (SLE); cold agglutinins causing vascular blockage due to agglutination of red cells; the use of heavy pneumatic drills disturbing neurovascular controls in the hands.

In these circumstances the disease is serious and disabling, the trophic changes adding significantly to the damage caused by the primary diseases elsewhere in the body.

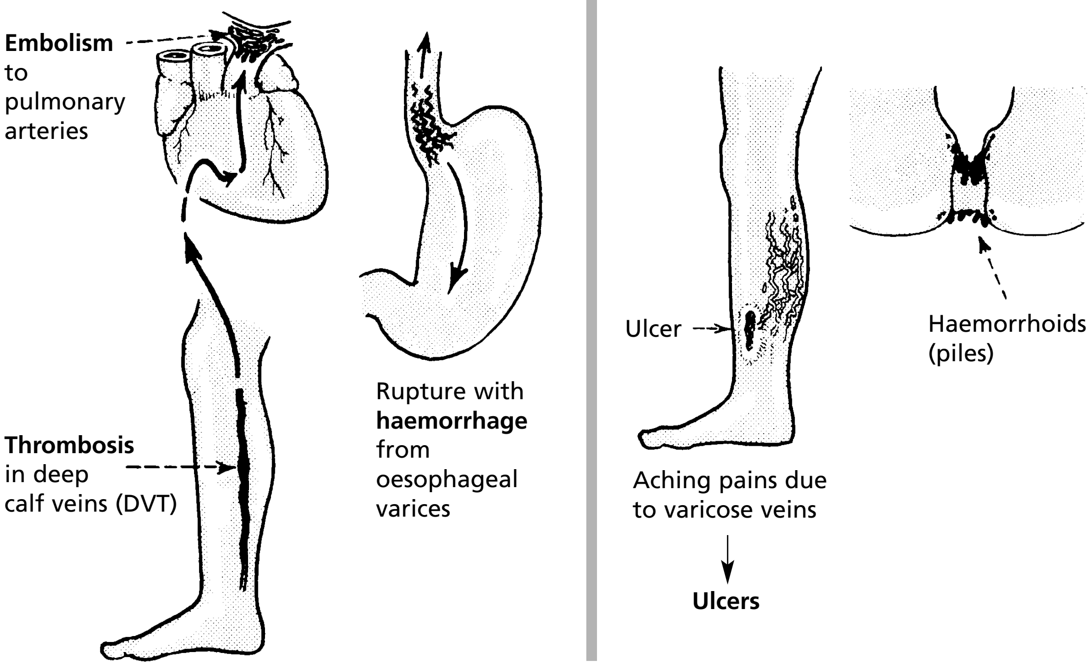


DISEASES OF VEINS

Diseases of the veins are important because they can be associated with:

1. ***Acute*** severe, sometimes fatal, complications

2. ***Chronic*** disability



DEEP VEIN THROMBOSIS AND THROMBOPHLEBITIS

The veins of the lower limbs are very common sites of acute thrombosis, especially after surgical operations and during illnesses with enforced bed rest.

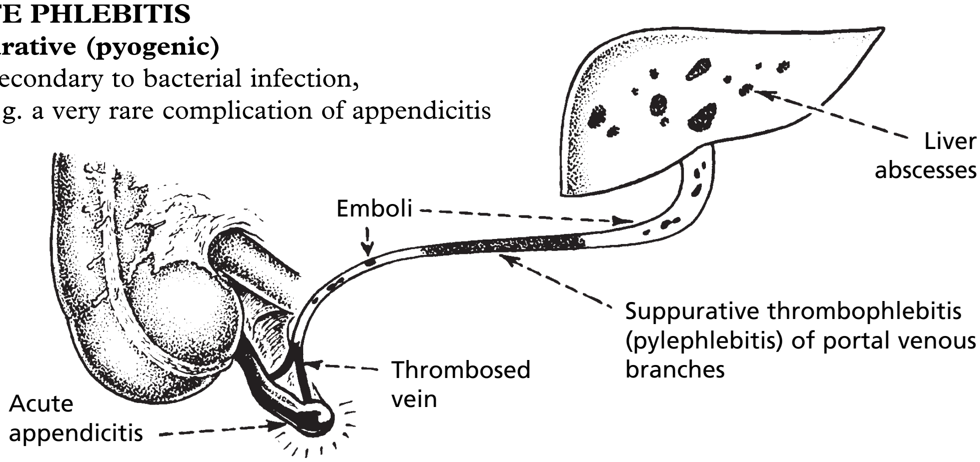
In the majority of cases the thrombosis is the primary event and mild inflammation follows as a reaction.

Thrombophlebitis is reserved for cases in which the thrombosis is secondary to inflammation in or adjacent to the vein.

ACUTE PHLEBITIS

Suppurative (pyogenic)

Secondary to bacterial infection,
e.g. a very rare complication of appendicitis

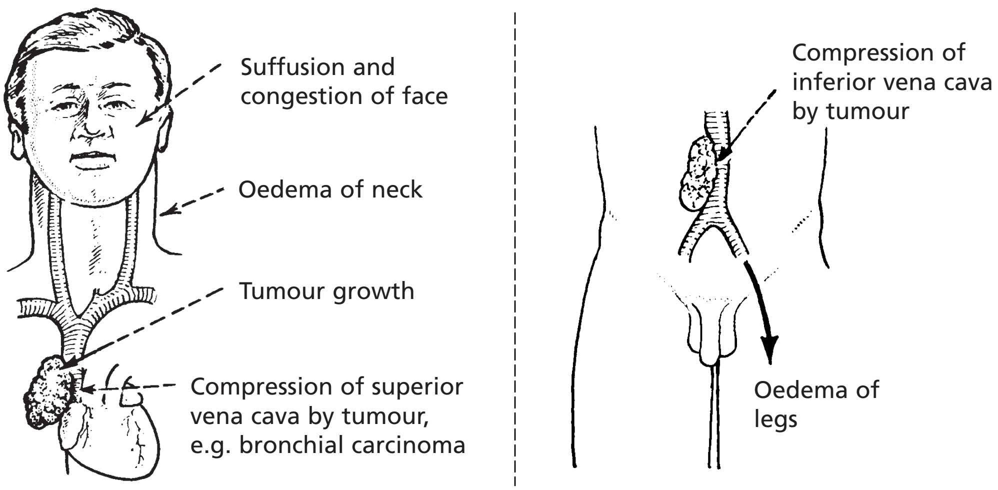


DISEASES OF VEINS

VEINS in MALIGNANT DISEASE

(a) Venules are easily invaded and infiltrated by carcinoma and are an important route in the metastatic spread of the tumour.
(b) Large veins, particularly in the mediastinum and pelvis, may be compressed from outside by the tumour – the resulting obstruction causing serious effects.

SUPERIOR VENA CAVA OBSTRUCTION



Migratory (thrombophlebitis migrans)

In this rare condition the thrombosis is not confined to the lower limb veins and can affect veins anywhere in the body. A striking feature is the appearance and disappearance of thrombosis apparently at random sites.

The mechanism is not fully understood but usually a **malignant tumour** is in the background – sometimes the phlebitis is the first clinical sign of an occult tumour but more often it complicates the terminal stages of tumour growth.

VARICOSE VEINS

This is a very common condition, the incidence increasing with **age**, and particularly high in **females** – often a sequel of pregnancy. The veins become prominent and tortuous and bulge outwards under the skin; the legs are particularly affected.

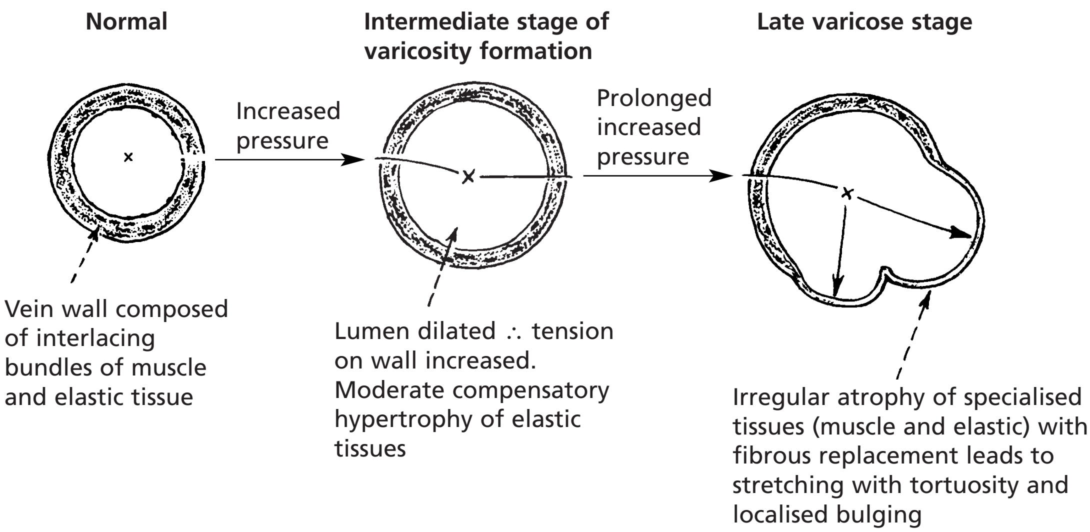
A **varix** is a localised bulge in a vein analogous to a saccular aneurysm in an artery. It is almost always associated with more generalised varicosity of the vein.

Aetiology

A vein wall, thin and composed of musculoelastic tissues, is designed to conduct blood at low pressures: the physiological movement of the blood is influenced mostly by pressure gradients derived from outside the vein wall.

Varicose veins arise when the vein wall is subjected to an increased expanding pressure (tension) over long periods.

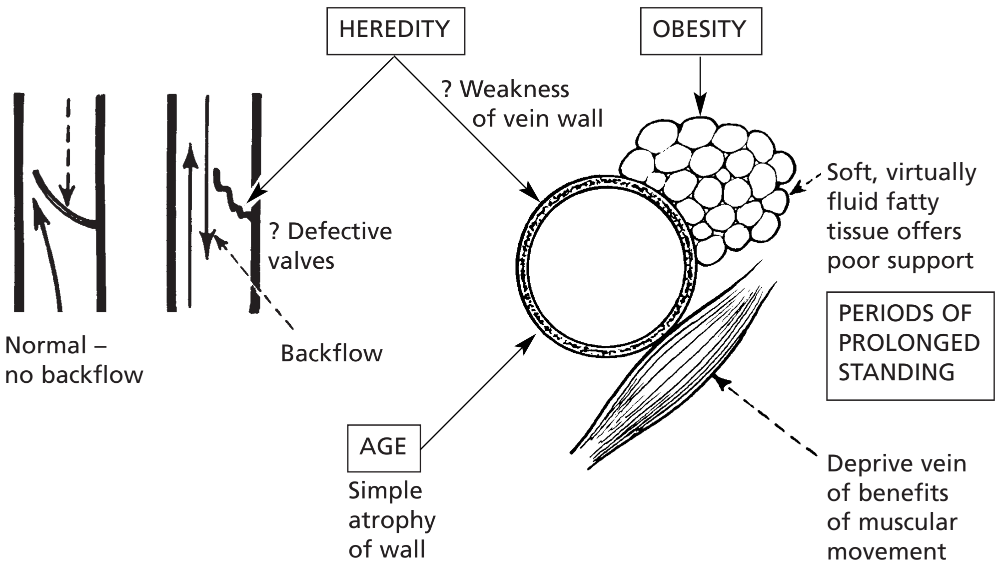
Mechanism



VARICOSE VEINS

FACTORS WHICH INFLUENCE THE BASIC MECHANISM

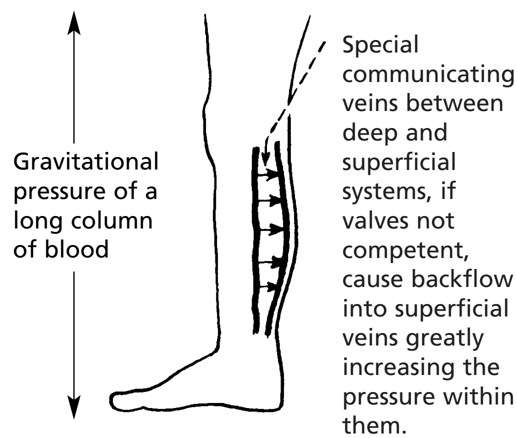
1. **Acting on the vein wall**



2. **Increasing the intraluminal pressure**

(a) Obstruction to venous flow – usually in the pelvis – by:
- Pregnancy
- Tumour
- Constipation with loaded colon
- Thrombosis in veins (also may destroy valves)
- Constrictions on limbs.

(b) Special anatomical considerations.



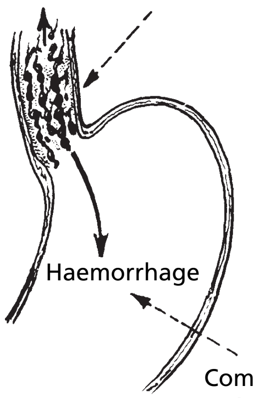
VARICOSE VEINS

Effects

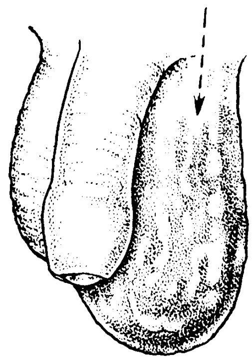
1. Fatigue and aching in legs.
2. Trophic changes – varicose eczema with pigmentation due to haemosiderin deposition – may proceed to ULCERATION: very slow to heal.
3. Haemorrhage is a rare complication.
4. Thrombosis is a frequent complication.
   Note: Superficial venous thrombosis is not usually associated with embolism; deep venous thrombosis is the dangerous condition.

VARICOSE VEINS IN SPECIAL SITES

Oesophageal varices



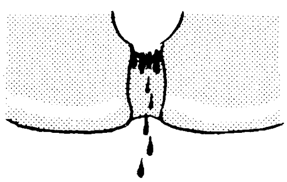
Usually due to portal venous obstruction when portal-systemic venous anastomoses open up.

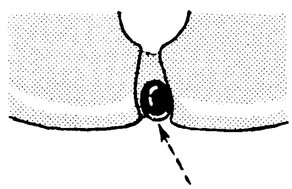


Affects the pampiniform plexus: feels like a 'bag of worms'. It may cause dull aching and, because the increased vascularity raises the scrotal temperature, the condition has been associated with infertility.

Haemorrhoids

Varices of the anorectal veins; usually associated with constipation.





Complications are: 1. rectal bleeding

2. acute pain due to local haematoma (not a true haemorrhoid).

3. Prolapse.

DISEASES OF LYMPHATICS

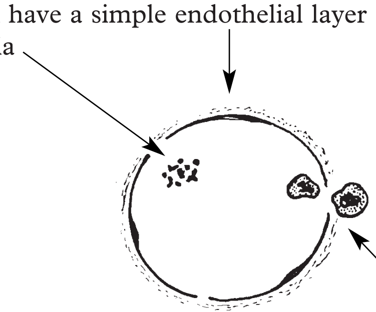
The lymphatic vessels participate in disease processes in two main ways:

1. They afford a natural route by which diseases can spread.
2. They may become obstructed, with serious results.

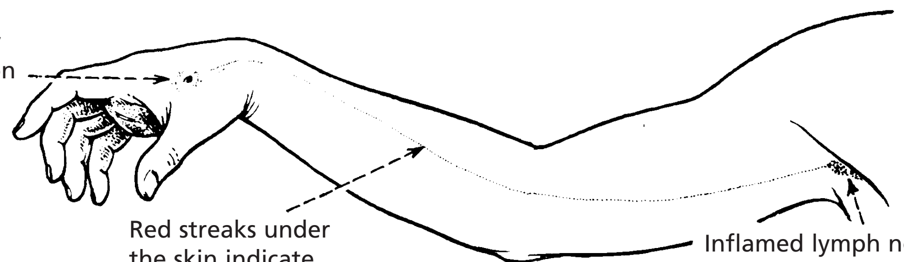
1. **LYMPHATICS as a mechanism by which DISEASE SPREADS**

Small lymphatics are thin-walled vessels which have a simple endothelial layer and readily allow entry of tumour cells, bacteria and foreign material often within phagocytes.

The mechanism is important in the spread of (a) infection and (b) tumours.



Acute lymphangitis
The lymphatics draining an area infected by pyogenic bacteria (especially streptococci) may themselves become acutely inflamed.

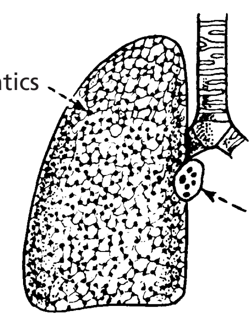


Chronic infections such as tuberculosis also spread by lymphatics.

Spread of tumours
This is an important route of spread of malignant tumours, especially carcinoma.

Disposal of particulate matter
This was formerly seen in the lungs where inhaled soot could be seen clearly indicating the lymphatic system under the pleura.

Soot (carbon) is relatively inert, but other dusts may cause serious disease.



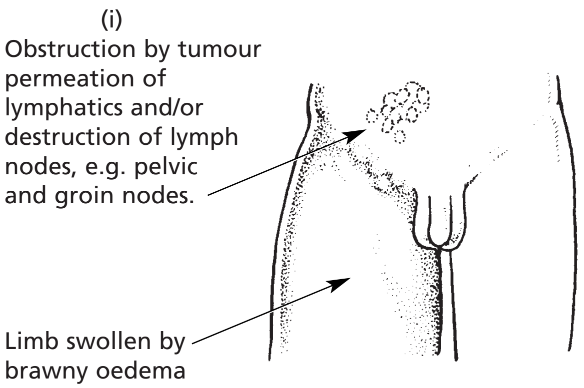
LYMPHATIC OBSTRUCTION

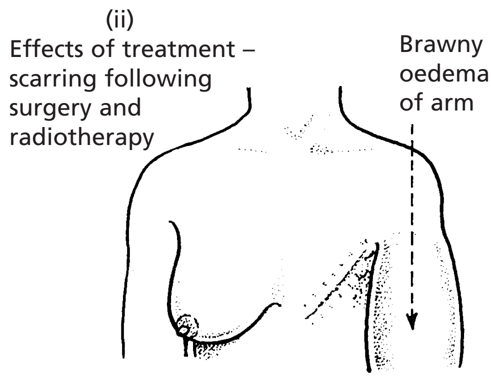
LYMPHATIC OBSTRUCTION

This is usually due to acquired disease but rarely there is a congenital deficiency of lymphatics (Milroy's syndrome).

The main causes of acquired obstruction are:

(a) **Tumour growth**





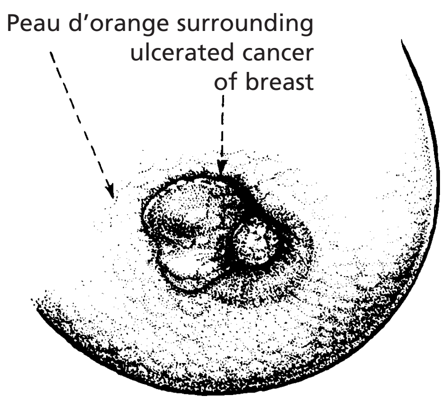
(b) **Blocking by parasites** – e.g. adult worms of filariasis in the tropics.

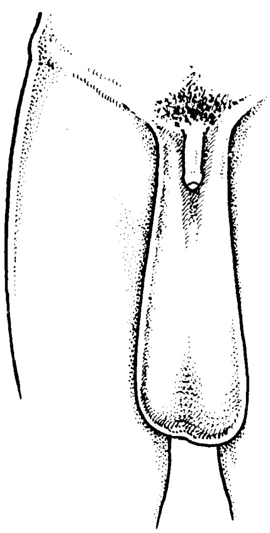
Effects of chronic lymphatic obstruction:
– accumulation of fluid in the tissues causes swelling of the affected part (lymphoedema).

Special varieties of lymphoedema

Peau d'orange – where the lymphatics of the skin are blocked by tumour.

Elephantiasis – where a limb and/or the scrotum is massively enlarged due to filarial lymphatic blockage.





VASCULAR TUMOURS

Benign tumours of endothelial cells – ANGIOMAS – illustrate the difficulty in defining the borderline between the tumours (neoplasms) and hamartomas (developmental abnormalities). These are discussed on page 132.

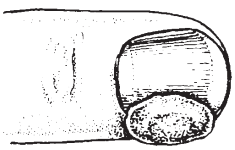
Other varieties include:

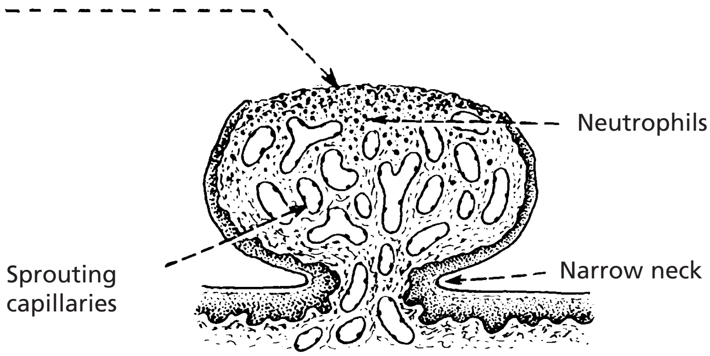
1. **PYOGENIC GRANULOMA**

This lesion appears on the skin at a site subject to trauma and infection, e.g. around the finger nails, the nostrils or the tongue.

It not uncommonly occurs during pregnancy.

It grows over several days to form a small red nodule up to about 1 cm in diameter and is usually ulcerated.





The lesion is benign despite its rapid evolution, and is cured by simple removal.

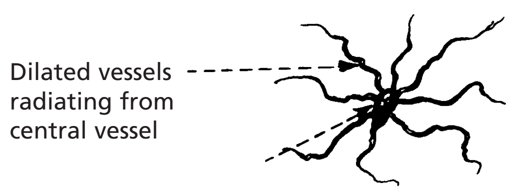
2. **TELANGIECTASIS**

Small localised dilatations of small blood vessels. There are two main types: congenital and acquired.

(a) *Congenital*. In the rare hereditary haemorrhagic telangiectasia, the small lesions occur in the skin and mucous membranes and may be associated with bleeding (especially from the nose).
(b) *Acquired*. The small lesions, affecting the face and neck, are known as **spider naevi**.

The mechanism of their development is probably related to oestrogen excess, since they occur in pregnancy and in serious liver disease (oestrogen catabolism diminished) where they are a diagnostic sign.

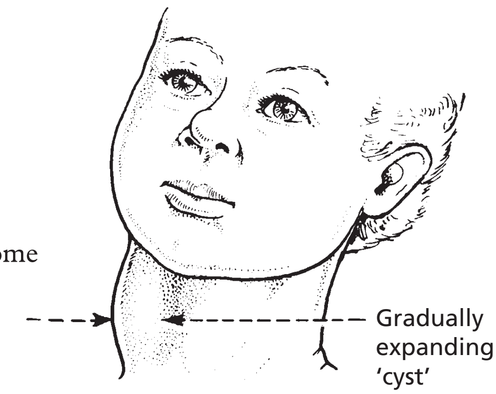
Telangiectasia may be seen in skin damaged by radiotherapy.



VASCULAR TUMOURS

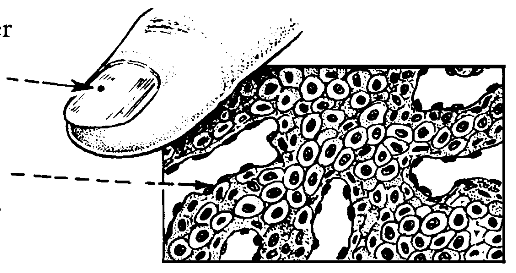
3. **LYMPHANGIOMA**

Lymphangiomas are much rarer than haemangiomas and are usually without serious pathological significance.



Occasionally the abnormal lymphatic vessels become distended and form fluctuant swellings with local pressure effects, e.g. 'cystic hygroma' of neck of babies and children.

4. **GLOMANGIOMA** (glomus tumour) – arises from a specialised type of arteriolovenous junction which includes a rich neural component. A common site is the finger tip, perhaps under the nail; a very small but often *painful tumour*.

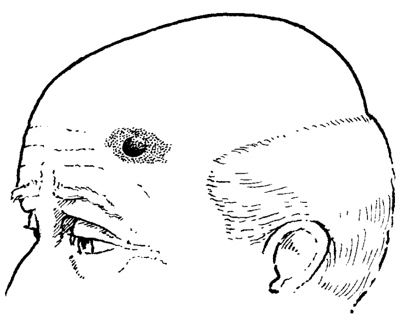


Microscopically it consists of a complex of blood vessels lined by endothelium but cuffed by round clear cells with contractile properties (myoid cells). It is rich in nerve fibres.

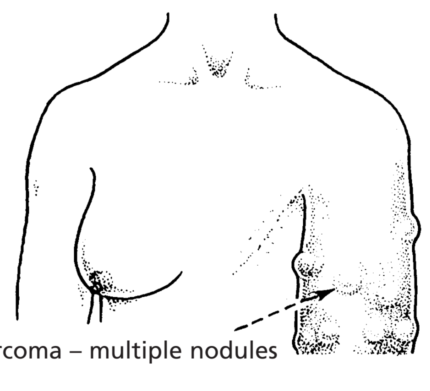
ANGIOSARCOMAS

These are uncommon malignant tumours of endothelial cells. They may affect the skin.

Lesions of the scalp occur in the elderly. They appear as spreading 'bruise-like' areas often with a central nodule. Chronic sun exposure is thought to be important.



Lesions often arise in the limbs in areas of lymphoedema e.g. in the past following irradiation and lymph node clearance for carcinoma of breast.



Angiosarcoma of the liver is associated with exposure to vinyl chloride monomer.

KAPOSI'S SARCOMA

This tumour has increased in incidence with the spread of AIDS and HIV infection.

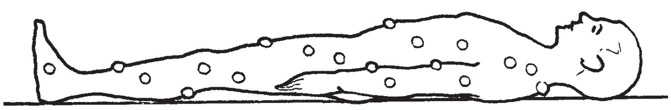
It is a tumour of endothelial cells due to infection by Herpes virus type 8 often occurring in immunocompromised patients.

It occurs in 4 groups of patients.

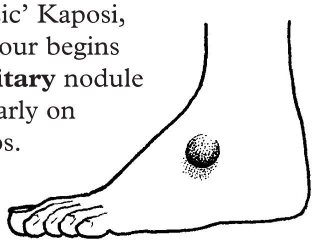
(a) **AIDS associated.**
(b) **Sporadic** (classic) – affecting elderly males (especially Askanazy Jews) living in the Mediterranean littoral.
(c) **Endemic** – mainly in central Africa, typically affecting young adults.
(d) **Iatrogenic** – in immunosuppression, e.g. transplant patients.

The disease presents as dark coloured (due to high blood content) **subcutaneous nodules** or plaques resembling bruises.

(a) The nodules may be **multiple** and fairly randomly distributed – this is seen particularly in AIDS cases.

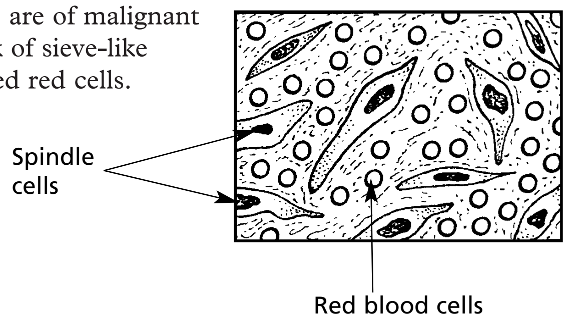


(b) In 'classic' Kaposi, the tumour begins as a **solitary** nodule particularly on the limbs.



(c) In the African endemic Kaposi, lymph nodes are commonly affected.

The histological appearances are of malignant spindle cells lining a network of sieve-like spaces containing extravasated red cells.



CHAPTER 8

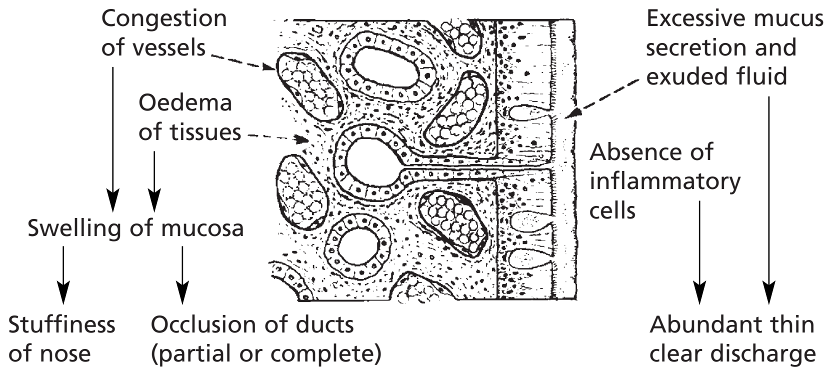
RESPIRATORY SYSTEM

UPPER RESPIRATORY TRACT

ACUTE INFLAMMATION

Infections of the nose, nasal sinuses, pharynx and larynx are common. They are usually mild and self-limiting. Most cases are due to viral infection, but this is often followed by bacterial superinfection.

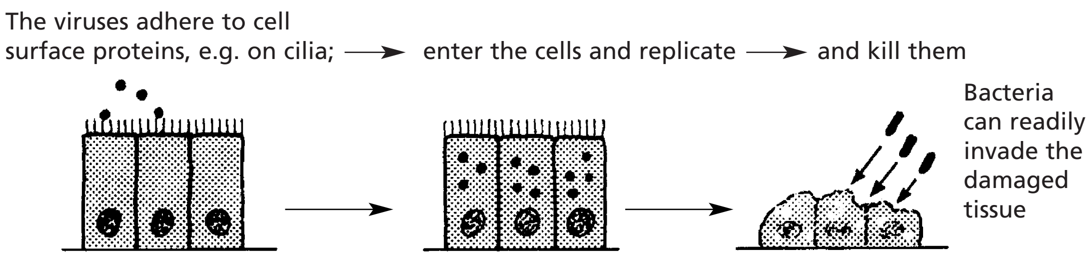
1. **Viral infection**
This phase is characterised by features of acute inflammation but without the exudation of neutrophils.



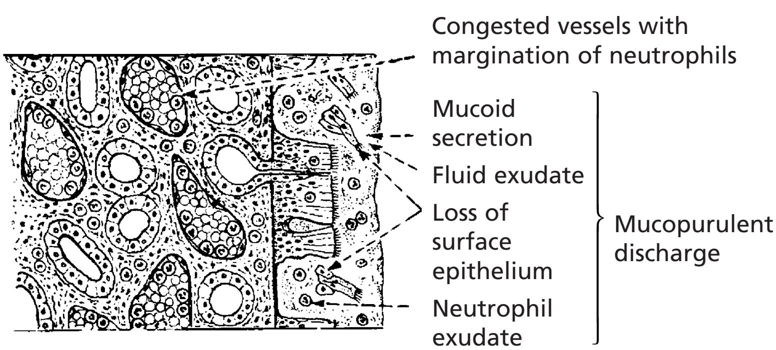
Viruses involved

A wide variety, of which the major types are:

(i) **rhinoviruses**
(ii) **coronaviruses** — responsible for more than half of cases of the common cold;
(iii) **myxoviruses,** (e.g. influenza), **paramyxoviruses** (e.g. respiratory syncytial virus) can also invade the lower respiratory tract.



2. **Bacterial phase**
Many bacteria are commensal in the respiratory tract (e.g. *Streptococcus mutans*, *Haemophilus influenzae*) and can superinfect the damaged tissue, which then exhibits the typical features of acute inflammation including exudation of neutrophils.



The wide variety of different viruses involved prevents protective immunity.

RHINITIS

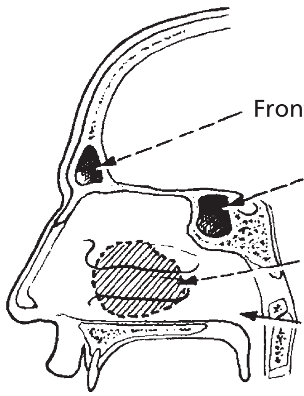
COMMON COLD (Acute coryza)

This common respiratory inflammation usually involves the nose and adjacent structures.

The 2 phases, *viral* and *bacterial,* are typically seen in this disease.

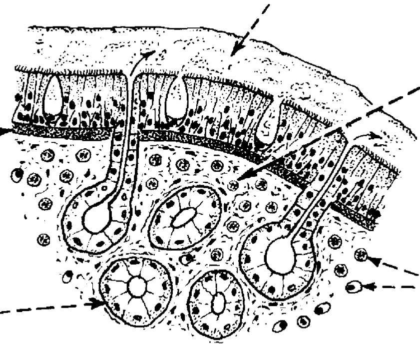
The drainage from the sinuses, especially the maxillary, is often blocked by swelling of the mucosa — giving rise to sinusitis.

The infection is acquired by droplet spread of viruses by sneezing.



ALLERGIC RHINITIS 'Hay fever'

An allergic (immediate type hyper-sensitivity) type of inflammation (p.101) is often seen. Patients develop immediate symptoms of sneezing, itching and watery rhinorrhoea.

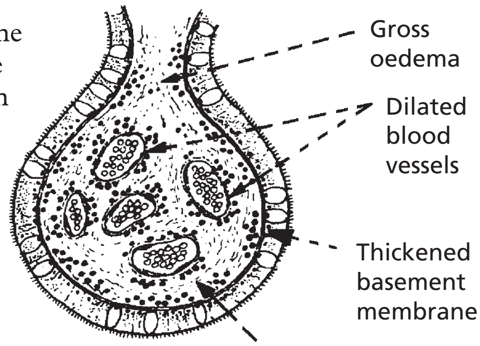


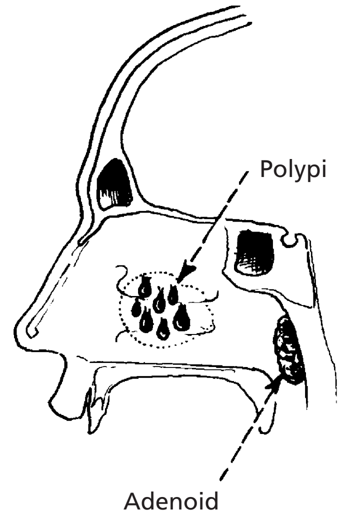
The repeated attacks frequently lead to chronic changes in the mucosa with polyp formation.

RHINITIS

NASAL POLYPS

These form particularly on the middle turbinate bones and within the maxillary sinuses.



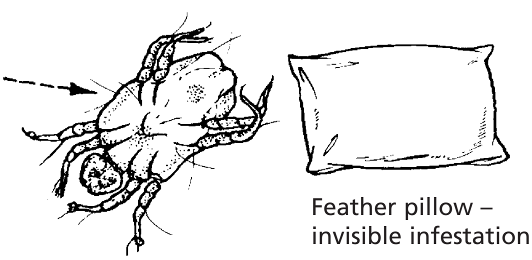


In the nasopharynx, the lymphoid tissue may be greatly enlarged (adenoids) and contribute to the nasal obstruction.

ALLERGIES

Seasonal allergy
This is due to pollens liberated from trees and grass.

Non-seasonal allergy
The main cause is the house dust mite, *Dermatophagoides pteronyssinus.* Allergy to pets is common, e.g. cats – the allergens are usually glycoproteins secreted by sebaceous glands and found in cat skin and saliva.



VASOMOTOR RHINITIS

This is a clinical diagnosis. The pathological changes are, to some extent, similar to those of allergic rhinitis, but the condition is more continuous, less spasmodic. Although the cause is unknown, viral infections in a polluted atmosphere (usually an urban setting) are thought to initiate the ‘sensitivity’ and non-specific stimuli such as bright light and smells precipitate an attack.

ACUTE PHARYNGITIS, TRACHEITIS AND LARYNGITIS

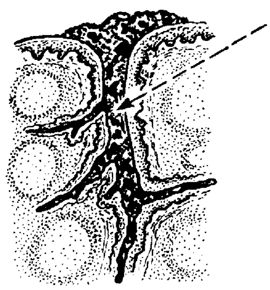
ACUTE PHARYNGITIS and TRACHEITIS

Most sore throats are caused by **viruses** – including adenovirus and Epstein–Barr virus.

Bacteria include *Streptococcus pyogenes, Haemophilus parainfluenzae* and *Corynbacterium diphtheriae.*

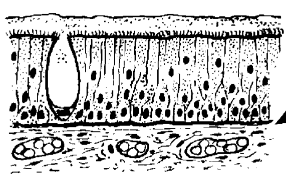
Tonsillitis is a common acute inflammation, historically due to streptococcal infection but, with the introduction of antibiotics, viruses are the initiating infective agents in most cases.
Acute phase ⟶ may progress to (a) acute suppuration (quinsy)
or (b) CHRONIC TONSILLITIS

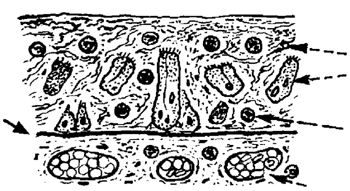




Diphtheria, now uncommon in countries where vaccination is widespread, is a serious infection.

The formation of a pseudomembrane is striking.





This pseudomembrane may spread to block the larynx, causing respiratory obstruction.

The EXOTOXIN of diphtheria is encoded by a bacteriophage (a virus which infects the bacterium). It can cause myocarditis (p.212) and neuropathy (p.569).

In **Acute epiglottitis**, typically due to *Haemophilus influenzae*, there is severe inflammation and oedema. In young children, the larynx becomes obstructed necessitating tracheostomy and administration of antibiotics.

Acute laryngitis is often due to parainfluenza viruses. Acute *oedema of the glottis* is seen in some cases of anaphylaxis (p.101) and angioneurotic oedema.

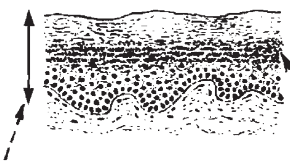
OTHER DISORDERS OF THE LARYNX

CHRONIC LARYNGITIS

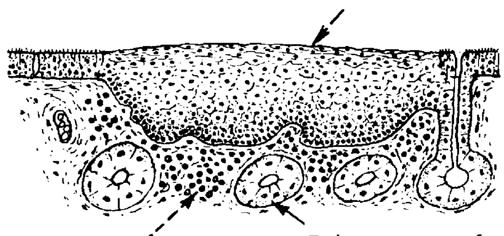
Cigarette smoking, repeated attacks of infection and atmospheric pollution may lead to chronic inflammation of the larynx.

Two main features are (a) changes in the lining epithelium and (b) increase in mucus secretion.

Vocal cords



Larynx



The following sequence of events tends to take place:

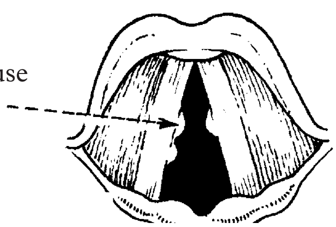
Chronic laryngitis → Squamous metaplasia → Loss of ciliary action → Retention of secretion

Chronic laryngitis → Mucous gland hyperplasia → Increased mucus secretion → Retention of secretion

Retention of secretion → Tendency to recurrent infection → Chronic laryngitis

Tuberculosis – this can cause severe ulceration of the larynx and is usually secondary to pulmonary tuberculosis.

Vocal cord nodule (singer's node)
This is found in singers and those who abuse their voice. Small smooth nodules may be seen on one or both vocal cords where the cords impact during phonation.



They consist of squamous epithelium overlying fibrin-rich and myxoid stroma.

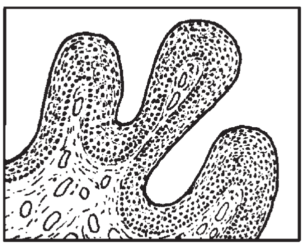
TUMOURS OF THE UPPER RESPIRATORY TRACT

BENIGN TUMOURS

(a) **Epithelial**

Papillomas may be single but are often multiple and due to infection by papilloma virus. The epithelium may be one of two types:

Squamous cell



Transitional cell



In transitional papillomas, the abnormal epithelium grows down the glandular ducts and the name 'inverted papilloma' is applied. Such tumours often recur after incomplete removal.

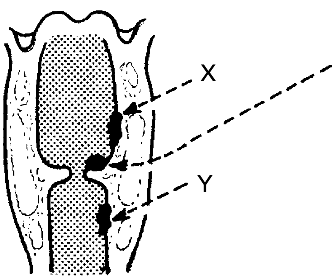
(b) **Connective tissue**

Haemangiomas, especially of the nasal septum, can cause persistent nose bleeds. A special form, angiofibroma, affects male children and grows throughout childhood but typically regresses.

MALIGNANT TUMOURS

These are mainly squamous carcinomas and are commonly seen in the larynx. Intraepithelial neoplasia (carcinoma-in-situ) is a frequent precursor.

Smoking and alcohol consumption are aetiologically important. The rate of growth and spread is influenced by the site within the larynx.



Tumours of the true cord tend to stay localised and have a better prognosis than supraglottic (X) and subglottic (Y) tumours – the looser surrounding tissues allow early local and cervical node spread.

Nasopharyngeal carcinoma is common in Eastern countries and is associated with Epstein–Barr virus infection.

Adenocarcinoma of the nose is a rare tumour, sometimes seen in woodworkers.

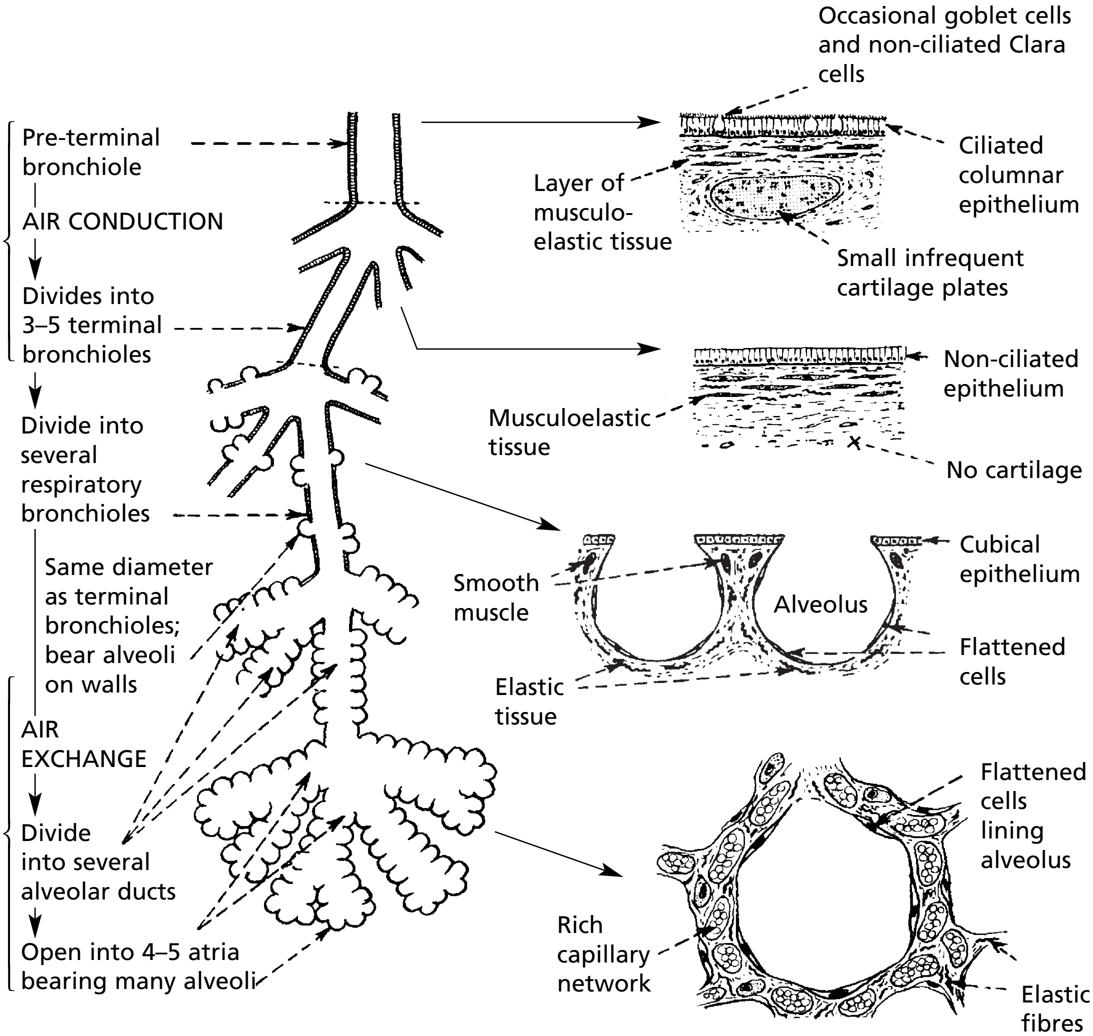
LUNGS – ANATOMY

ACINUS

This is the functional unit of the lung, where gas transfer takes place. It consists of the respiratory bronchiole and associated alveolar ducts and sacs supplied by one terminal bronchiole. There are approximately 25 000 acini in the normal adult male lung.

LOBULE

This is served by one preterminal bronchiole and is the smallest anatomic compartment of lung that is grossly apparent. It contains 3 to 30 acini and is bound by connective tissue septa. These connective tissue septa may be accentuated in smokers.



The total area for air exchange is very large (equivalent to a tennis court) allowing considerable reserve capacity.

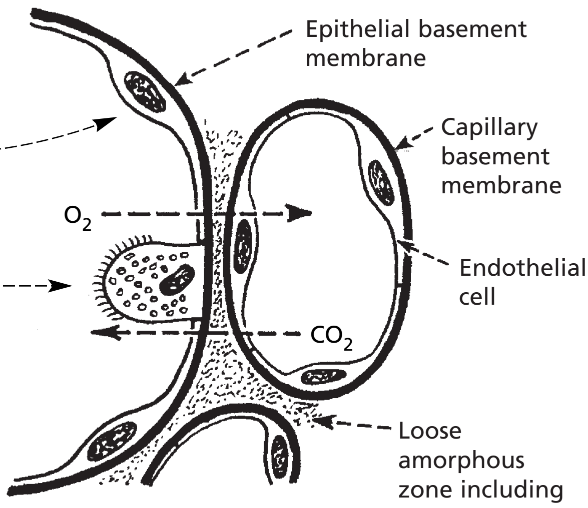
LUNGS – ANATOMY

HISTOLOGY of the ALVEOLUS

Two types of cell (pneumocytes) line the alveoli:

Type 1
are flattened cells which cover >90% of the surface.

Type 2
These rounded granular cells secrete surfactant and undergo hyperplasia when Type 1 cells are injured. They also act as progenitors for Type 1 pneumocytes.

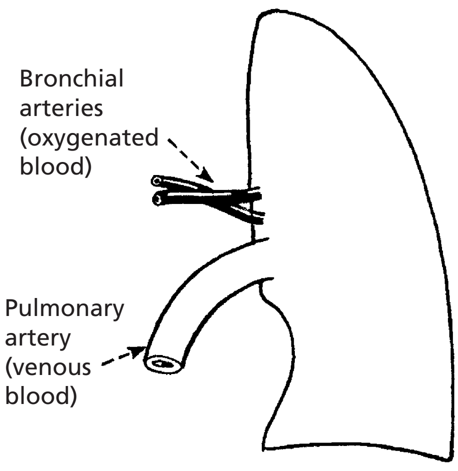


These relationships allow rapid diffusion of O_2 and CO_2

Macrophages and mast cells are also present in the alveoli.

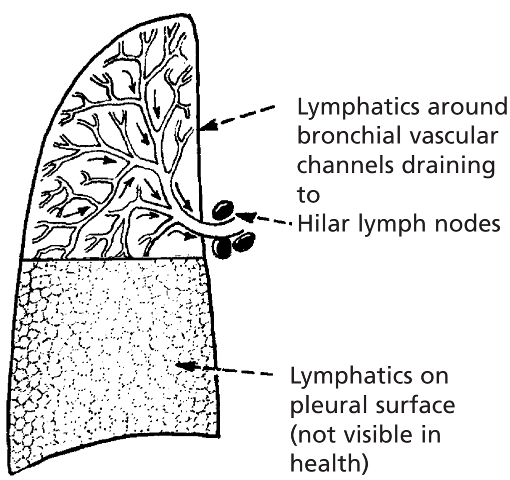
PULMONARY VASCULATURE

Dual blood supply



This dual supply is of importance when a pulmonary arterial branch is blocked.

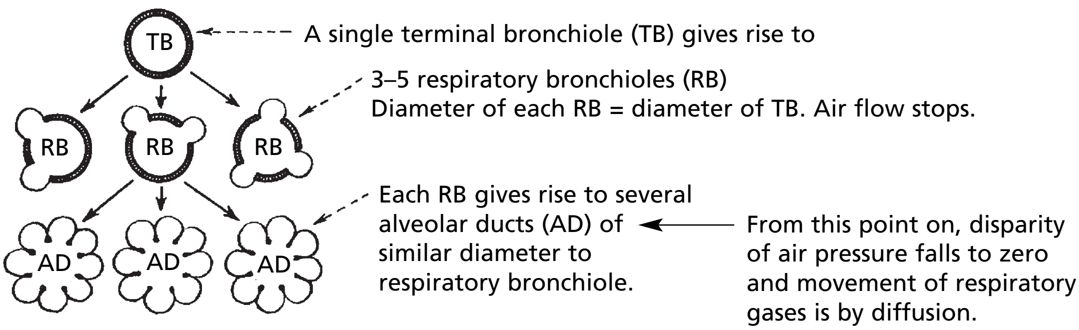
Lymph drainage



This fine network of lymphatics becomes visible when pigmented dust is inhaled over long periods.

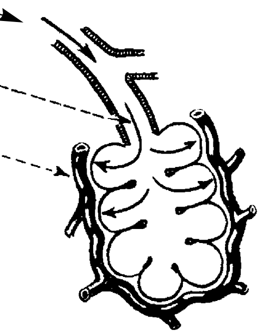
RESPIRATION

The normal intake of air is around 7 litres per minute; of this, after allowing for non-functioning dead space (trachea, bronchi, etc.), approximately 5 litres per minute are available for alveolar ventilation. A definite flow of air is maintained as far as the terminal bronchiole. Beyond this point the actual flow ceases and gas exchange is effected by diffusion.



Three factors are involved in the maintenance of adequate respiration:

1. Adequate intake of air
2. Rapid diffusion along alveolar ducts and through alveolar walls
3. Adequate perfusion of pulmonary circulation



Interference with any of these factors will result in respiratory embarrassment (dyspnoea) and even respiratory failure.

Inadequate air supply to alveoli (hypoventilation)
This may be due to lesions and diseases which interfere with the mechanics of respiration, such as central nervous lesions affecting the respiratory centre, paralysis of muscles of respiration as in poliomyelitis, injuries and deformities of the thoracic skeleton (e.g. fracture of ribs, kyphosis) and pleural disease preventing lung expansion as in pleural effusion or pneumothorax.

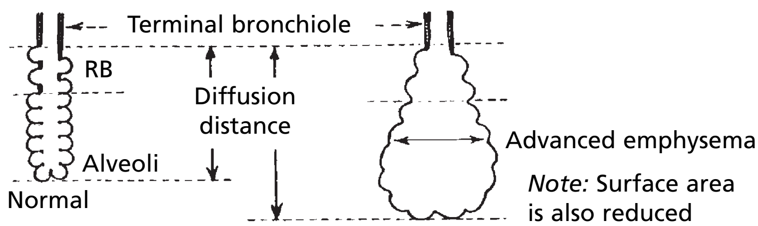
The most common cause of hypoventilation is bronchial obstruction. This may be reversible due to bronchial spasm as in asthma or irreversible in chronic obstructive pulmonary disease (p.258).

RESPIRATION

Impaired diffusion of gases

Three mechanisms may interfere with diffusion:

1. Reduction in the total alveolar surface available for diffusion, e.g. consolidated airless lobe in pneumonia, fibrosis of lung or tumour growth.
2. Increase in distance over which diffusion takes place as in emphysema.



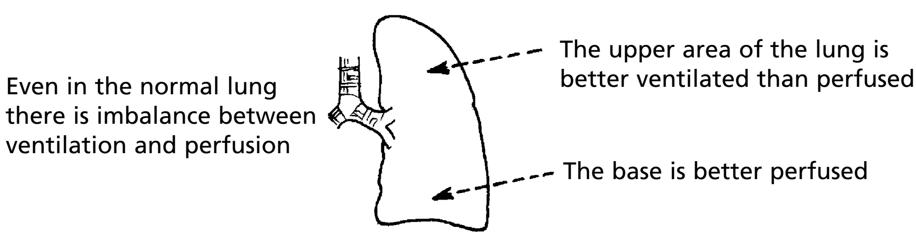
3. Increase in the thickness of the alveolar capillary membrane. Diffusion of gas across the membrane is so rapid this can be of little practical importance. CO_2 is more soluble than O_2 and diffusion through the alveolar wall is 20 times as rapid as O_2, therefore while blood O_2 progressively falls there is usually no retention of CO_2.

Altered pulmonary perfusion

Interference with the pulmonary circulation may occur in 4 main ways:

1. Occlusion of larger vessels by multiple emboli.
2. Slowing of the pulmonary circulation as in venous congestion due to left heart lesions or congenital left-right shunts.
3. Reduction in the pulmonary capillary bed by diffuse lung disease such as fibrosis or emphysema.
4. Pulmonary vascular spasm due to hypoxia. Permanent changes can occur in the vessels if the hypoxia is unrelieved.

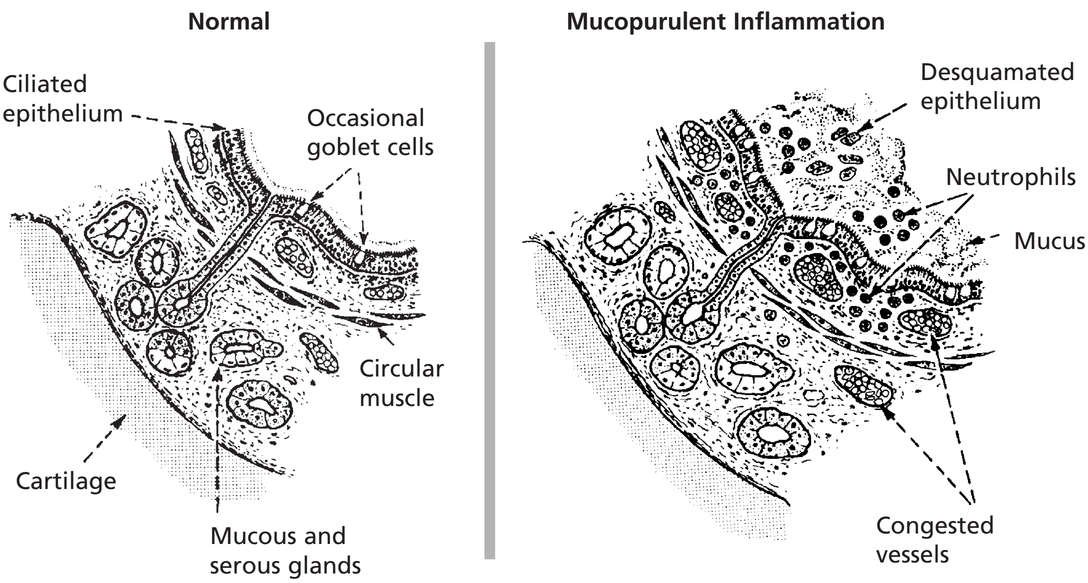
Note: In addition to hypoxaemia, inadequate perfusion tends to cause retention of carbon dioxide.
In chronic lung disease, ventilation, diffusion and perfusion disorders are present in varying degrees.



In many lung diseases this imbalance is increased. Admixture of well and poorly oxygenated blood results in hypoxaemia.

ACUTE BRONCHITIS

This is an inflammation of the large and medium bronchi. The condition may be serious if associated with pre-existing respiratory disease. Mucous and serous glands in the walls of the bronchi provide abundant mucoid secretion during the inflammation. Ciliated epithelia lining the bronchi aid passage of the exudate upward and help prevent spread down to the bronchioles.



In most cases, the process is initiated by a viral or mycoplasmal infection. It is a common complication of influenza and measles. This initial phase is followed by bacterial invasion. *Streptococcus pneumoniae* and *Haemophilus influenzae* are commonest, but *Staphylococcus aureus* and *Streptococcus pyogenes* may be found, especially in infants.

The condition is usually mild, and spread to the bronchioles is unusual in healthy adults due to the effective ciliary action of the bronchial epithelium. Spread may occur however in debilitated people. Bronchiolitis and bronchopneumonia result and can prove fatal. Equally important is the serious effect of repeated attacks of acute infection in patients with CHRONIC BRONCHITIS (p.258).

In **children:**

1. Whooping cough (due to *Bordetella pertussis*) may cause permanent damage due to the severity of the infection and the stress on the airways during the coughing and whooping attacks.
2. **Bronchiolitis** in the very young (<2 years), in the majority of cases, is due to *Respiratory Syncytial Virus* and the risk of progression to **bronchopneumonia** is high.

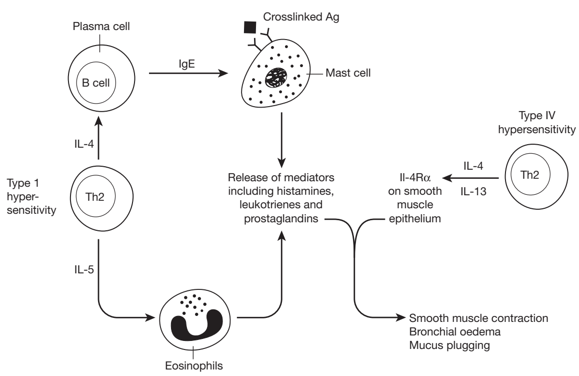
BRONCHIAL ASTHMA

In asthma, there are spasmodic attacks of reversible bronchial obstruction with wheezing and dyspnoea and often a dry cough. The prevalence has markedly increased in recent years, although has now plateaued. There are 2 main patterns:

1. **Atopic asthma** (p.102)
   – typically starts in childhood.
   – often a strong family history of asthma or atopic conditions (e.g. eczema).
   – attacks provoked by predominantly IgE type I hypersensitivity reaction to inhaled allergens, e.g. pollen, cats, house mite dust.

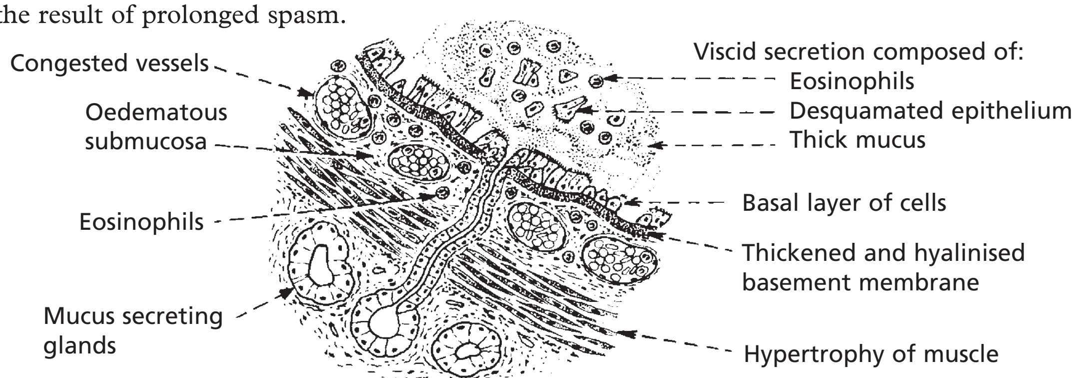
2. **Non-atopic asthma**
   – usually in middle age.
   – usually no history of atopy: family history uncommon.
   – no particular antigens incriminated.

Other varieties include occupational asthma and aspirin-induced asthma.
The basic mechanism is as follows:



ACUTE ASTHMA
Recurrent episodes of inflammation lead to irreversible damage

The **histological changes** are a combination of allergic reaction and muscular hypertrophy, the result of prolonged spasm.

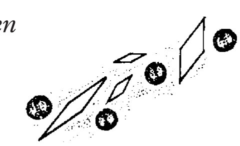


Sputum
In some cases the following may be seen:

1. *Curschmann's spirals* – appear as small white granules in sputum.



2. *Charcot–Leyden crystals* – in association with eosinophils.



CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

This term describes three entities that show considerable clinical overlap:
1. Chronic bronchitis
2. Emphysema
3. Small airways disease

COPD is common and is the fourth leading cause of death worldwide.

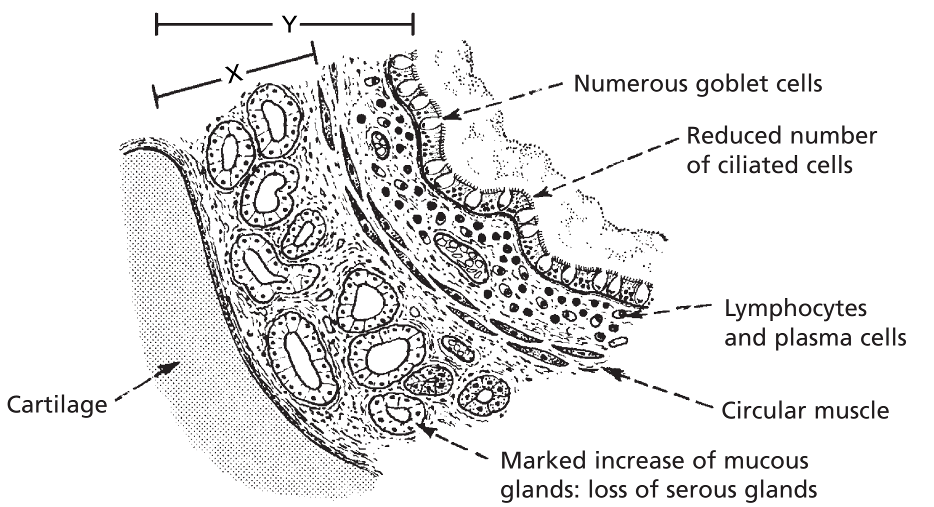
Aetiology The main factors are:
1. SMOKING – by far the major risk factor and dose related.
2. α_1-antitrypsin deficiency. Reduced levels of this protease inhibitor correlate with lung damage, especially in smokers.
3. OCCUPATION, especially exposure to dusts, e.g. coal mining.

CHRONIC BRONCHITIS

The clinical definition is based on the presence of a productive cough lasting at least 3 months and occurring annually for at least 2 years.

Pathologically the following changes are seen:

The increase in thickness of the mucous gland layer is striking: at post-mortem the Reid index is measured – i.e. the ratio of the submucous layer (X) to the whole thickness (Y): a value greater than 1:2 is significant.



The effect of these changes is:

Increase in goblet cells + Increase in mucous glands → Large quantity of viscid secretion ← Loss of ciliated epithelium

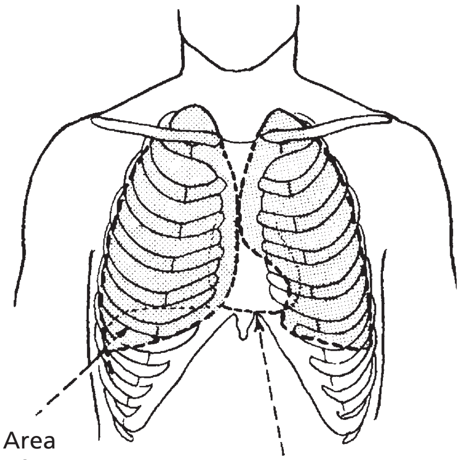
Large quantity of viscid secretion →
- EPISODES of ACUTE BRONCHITIS – these may precipitate respiratory failure and often cause death.
- COUGH and SPUTUM

EMPHYSEMA

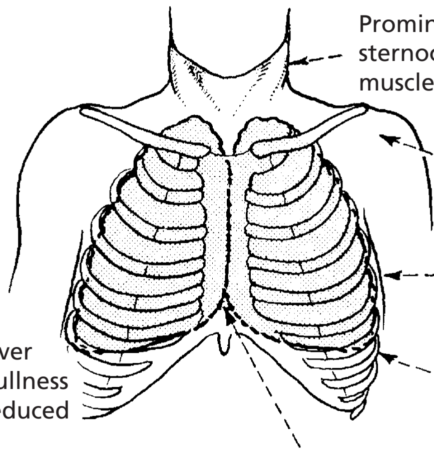
This is defined as a permanent dilatation of air spaces distal to the terminal bronchiole due to destruction of their walls without fibrosis. It is an important component of COPD (p.258) and has the same aetiological factors.

Changes seen on clinical examination

Normal

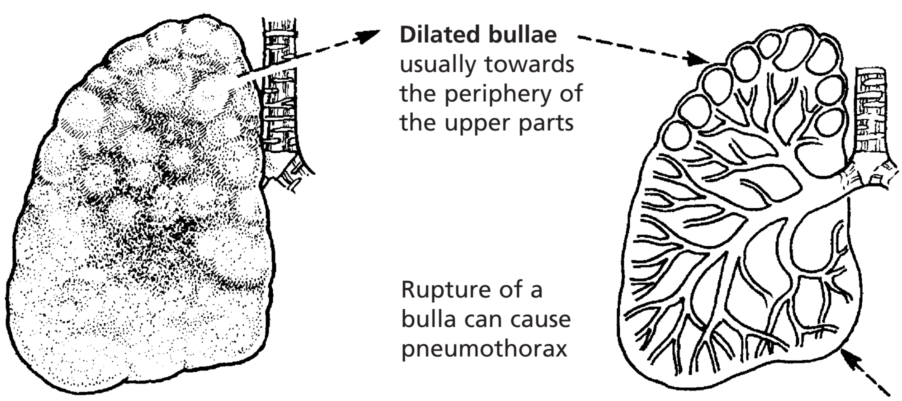


Anatomical changes due to increased use of accessory muscles of respiration and increased lung volume.



Pathological changes At post-mortem the lungs are over-inflated

When removed the lung tends to collapse unless it is inflated with fixative and cut later.

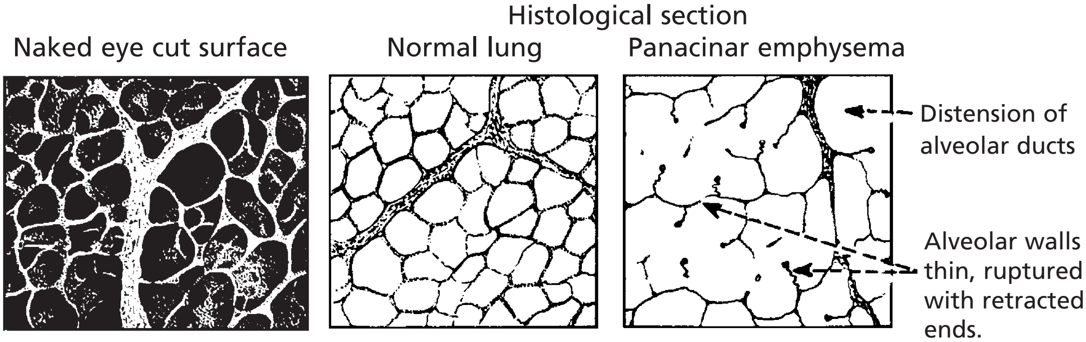


On the sectioned lung 2 main patterns are seen.
1. **Panacinar emphysema** and 2. **Centriacinar (centrilobular) emphysema.**

EMPHYSEMA

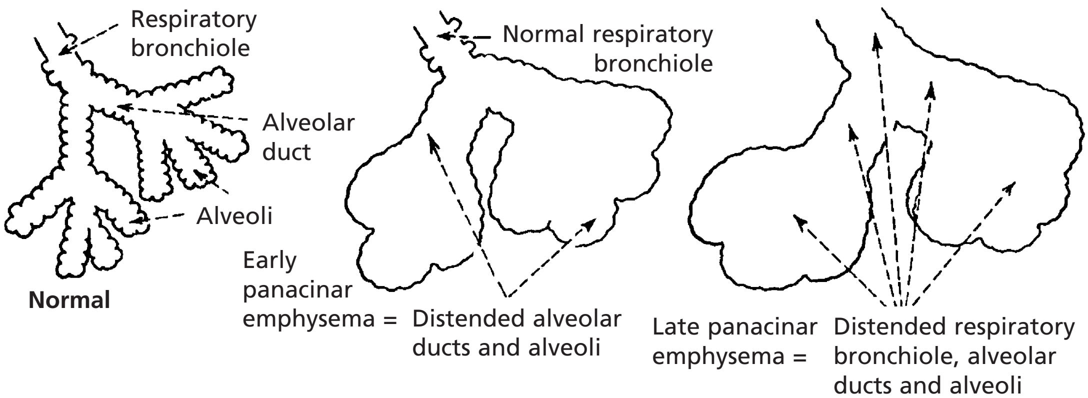
PANACINAR EMPHYSEMA

The enlarged air spaces are distributed across the entire acinus.



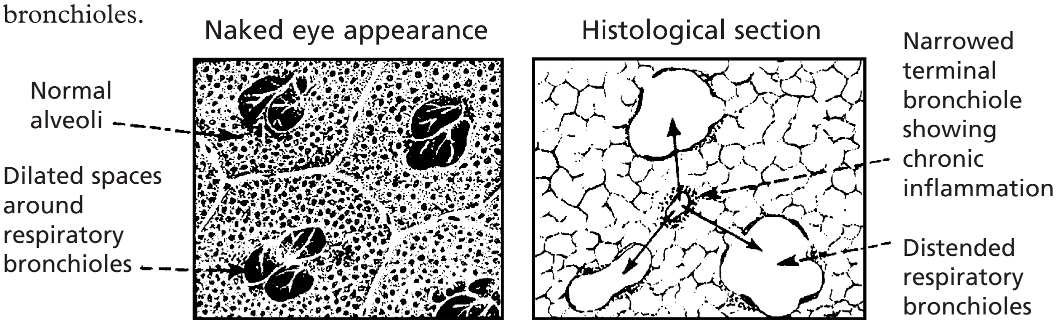
Special stains show loss of elastic tissue. The capillaries are stretched and thinned. The reduction in blood supply is probably a factor in leading to rupture of alveoli.

There is little evidence of bronchiolitis. The voluminous lungs produce characteristic radiological changes. The distension eventually spreads to involve the respiratory bronchiole, i.e. the whole acinus is affected – panacinar emphysema.



CENTRILOBULAR EMPHYSEMA

In this form the dilated air spaces immediately surround and involve the respiratory bronchioles.



Chronic inflammation of the respiratory bronchioles is an important feature: eventually, in many cases, the distension extends to produce panacinar emphysema.

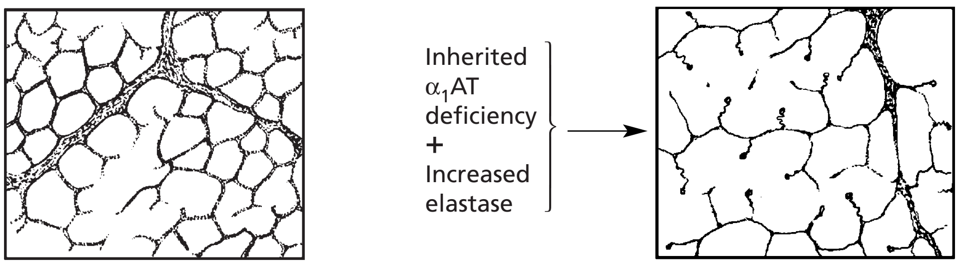
EMPHYSEMA

Pathogenesis

In emphysema alveolar destruction is the result of several processes:

(1) *An imbalance between protease and antiprotease activity.* This may occur due to:

(a) Reduced inhibitor in α_1-antitrypsin deficiency (inherited in an autosomal codominant pattern.



Normal lung

Gradual development of panacinar emphysema

(b) Excess enzyme production, e.g. due to smoking → inflammation of bronchioles → ↑ proteases → centrilobular emphysema.

(2) *Innate immunity*

Alterations in Toll like receptor 4 may result in persistent low grade activation of the innate immune system and destruction of lung tissue.

(3) *Cellular senescence*

Cigarette smoke upregulates genes involved cellular senescence and affected cells may undergo apoptosis.

Emphysema is an important component of lung damage due to dust inhalation (*pneumoconiosis*) (see p.272).

FUNCTIONAL EFFECTS OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

Patients with COPD tend to fall into 2 groups depending on whether or not they tolerate hypoxia.

(a) PINK PUFFERS
Do NOT tolerate hypoxia.
Severe breathlessness.
Hyperventilation.
Relatively normal blood gases.

(b) BLUE BLOATERS
Tolerate hypoxia.
Severe hypoxaemia and hypercapnia.
Right ventricular hypertrophy.
Cor Pulmonale with peripheral oedema.
Secondary polycythaemia.

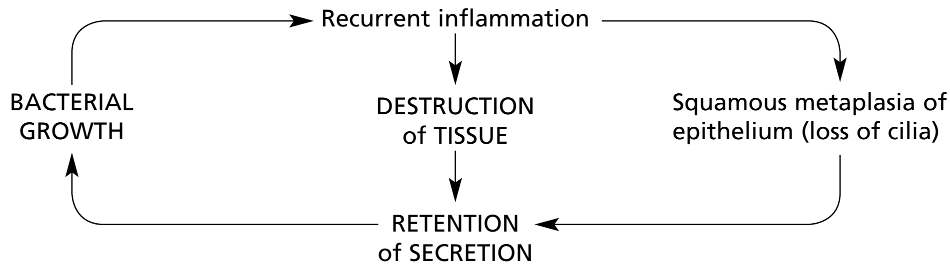
Eventually many patients develop severe chronic respiratory failure and may die during an acute episode of bronchitis.

BRONCHIECTASIS

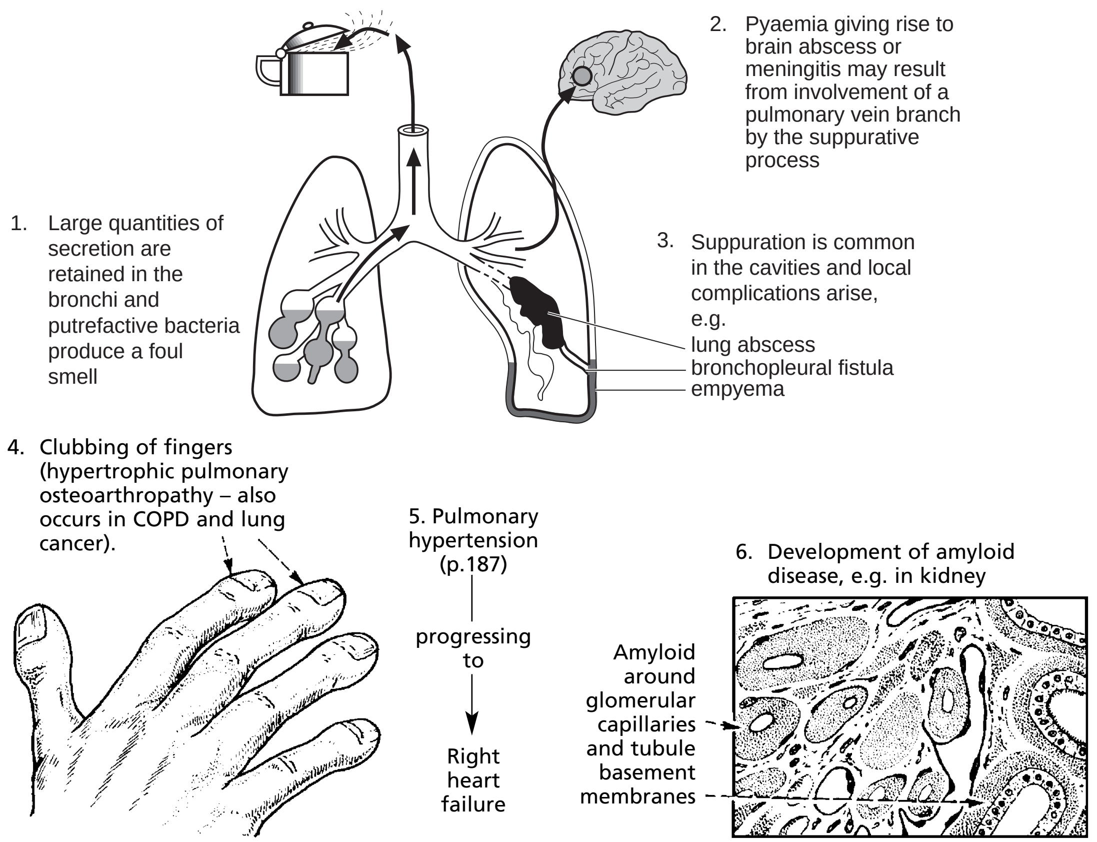
Bronchiectasis means a permanent dilatation of one or more bronchi. There are 2 main subdivisions

1. ***Obstructive*** due to tumour, foreign body or enlarged lymph nodes
2. ***Post-infective*** due to repeated respiratory infection, e.g. Cystic Fibrosis or immunodeficiency syndromes.

Pathogenesis



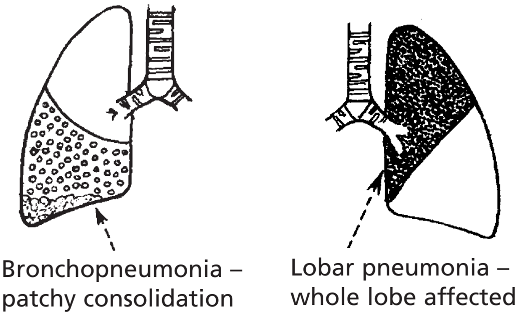
Effects



PNEUMONIA – BRONCHOPNEUMONIA

Pneumonia is an inflammatory process involving the alveolar tissue of the lungs. It is discussed under 3 main headings:

1. Bronchopneumonia
2. Lobar pneumonia
3. Miscellaneous pneumonias

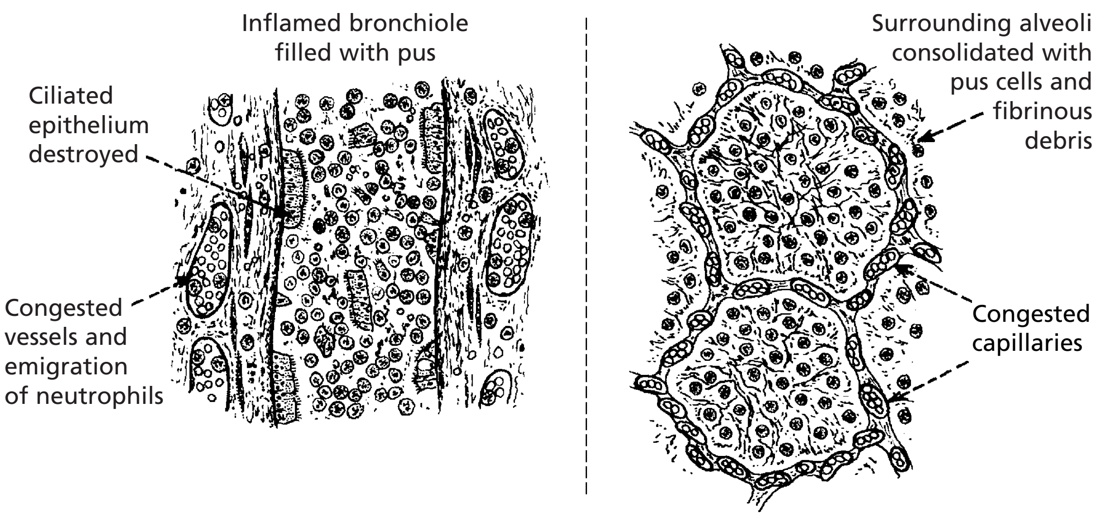


1. BRONCHOPNEUMONIA

Bronchopneumonia caused by a variety of bacteria is the commonest form. It may affect all ages, but it is particularly frequent in 4 circumstances:

(a) as a terminal event in a chronic debilitating disease
(b) in infancy
(c) in old age
(d) as a manifestation of secondary infection in viral conditions, e.g. influenza, measles.

Bronchopneumonia is primarily an inflammation spreading from terminal bronchioles to their related alveoli.
The lesions are initially focal, involving one or more lobules.
First red, then grey, they show a central bronchiole containing pus.



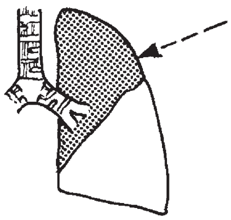
Possible sequels

1. Resolution – complete or partial (antibiotic and physiotherapy are important).
2. Patchy scarring.
3. Rarely, continuing sepsis with lung abscess formation.

LOBAR PNEUMONIA

2. LOBAR PNEUMONIA

As the name suggests, a complete lobe or even two lobes of a lung are affected, the most striking changes occurring in the alveoli. The disease is now rare in Western countries. It is seen typically in adults aged 20–50 years with males predominating and is caused by *Streptococcus pneumoniae*. Occasionally *Klebsiella pneumoniae* is the agent in the debilitated elderly, diabetics and alcoholics.



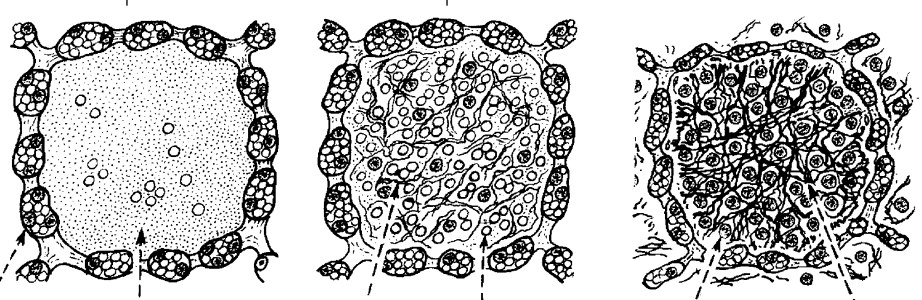
The whole affected lobe progresses uniformly through 4 distinct phases illustrating the classic progression of an acute inflammation: this has been so radically altered by antibiotic treatment that the following description is to some extent historical.

Clinically, the onset is acute with fever and often rigors. There is a dry cough and rusty sputum; dyspnoea and often chest pain due to pleurisy.

The **Pathology** is described in 4 phases merging sequentially: all the alveoli in the lobe are uniformly affected.

	Phase 1 CONGESTION	**Phase 2** RED HEPATISATION	**Phase 3** GREY HEPATISATION
Time	1–2 days	2–4 days	4–8 days
Gross appearance	Lungs are dark red and wet	Lungs are solid, RED and dry	Lungs are solid and GREY (due to high concentration of neutrophils)

Microscopic appearance



Phase 4 – RESOLUTION begins dramatically on day 8–10 and restoration to normal is rapid.

LEGIONNAIRE'S DISEASE

Previously confused with pneumococcal pneumonia, Legionnaire's disease occurs in small epidemics, is more common in males and is due to a tiny Gram-negative bacillus – *Legionella pneumophila*. The death rate can be high – up to 20%. Infection is associated with inhalation of aerosol from contaminated water storage systems.

Clinical features
Two phases are recognised:

Prodromal phase – vague flu-like illness lasting about 5 days.

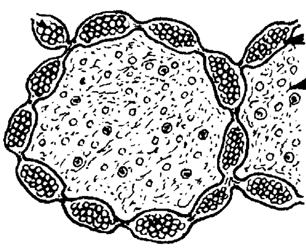
Active phase
A dry cough develops. There is pyrexia and the patient may become seriously unwell with confusion.
Signs of consolidation appear. Severe vomiting and diarrhoea may develop.

Laboratory findings
Hyponatraemia. Lymphopenia. Neutrophils normal.
Signs of disseminated intravascular coagulation may develop. The most useful diagnostic tests are to detect the bacteria in sputum or *Legionella* antigens in urine. Serology may show an increase in antibody titre after 10–15 days.

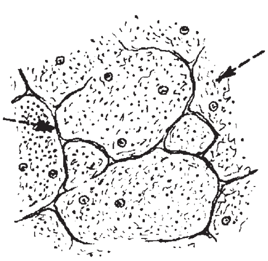
Pathology
Both lungs are consolidated, dark red, heavy and oedematous. Fibrinous pleurisy or pleural effusion may be found.

Histology
Two stages are evident:

First stage



Second stage



The exudate may organise, causing an increasing interstitial fibrosis with permanent loss of lung function.

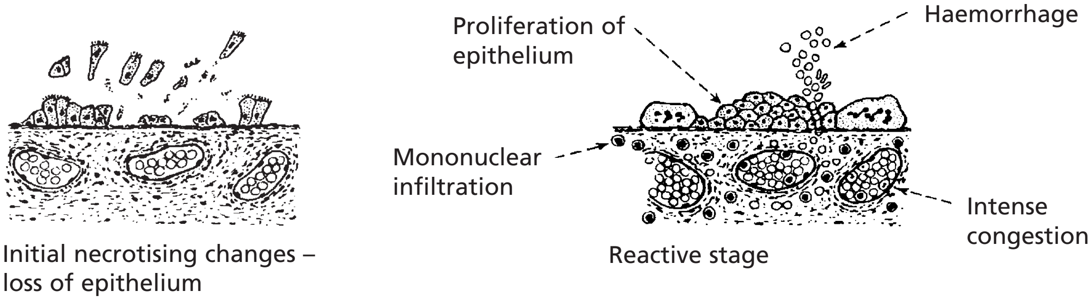
VIRAL PNEUMONIAS

INFLUENZA

In most cases, influenzal infection is confined to the upper respiratory tract, but in debilitated persons and during epidemics, the whole respiratory tract is affected.

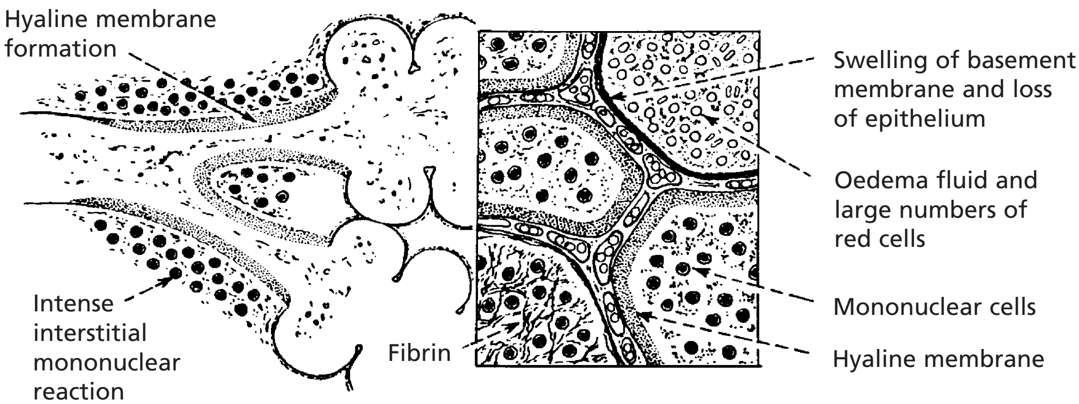
Trachea and bronchi

Intense inflammation with haemorrhage develops.



Pneumonia changes

The lungs are bulky, purple red and exude blood-stained froth when cut. The microscopic changes vary from one part to another.



Infective agents

Of the three main types A, B and C, type A is the most virulent, and mutants of this type are responsible for most epidemics and the fatalities which occur. The 2009 pandemic was due to a swine influenza of type A known as H1N1. Severe disease and death was more common in children and pregnant women.

Secondary infection is common, the bacteria most frequently involved being *Staphylococcus aureus, Haemophilus influenzae* and *Streptococcus pneumoniae*.

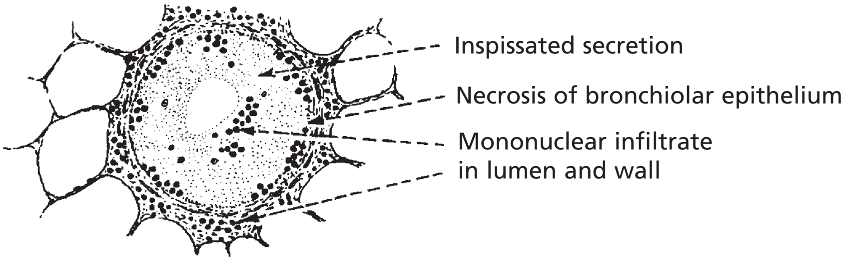
SARS

Severe acute respiratory syndrome is a recently recognised infectious atypical pneumonia caused by a novel corona virus, the SARS-associated corona virus. The disease was first recognised in Asia in February 2003 and caused a pandemic over the ensuing months.

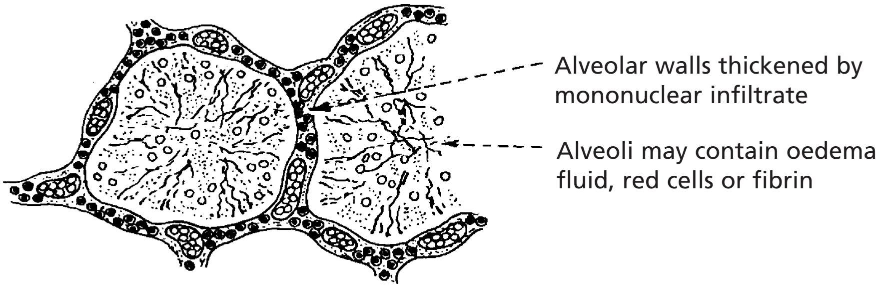
ATYPICAL PNEUMONIAS

There are a number of pneumonic conditions due to *viruses* and *bacteria* in which a common pattern of pathological change is observed.

1. **Necrotising bronchiolitis**

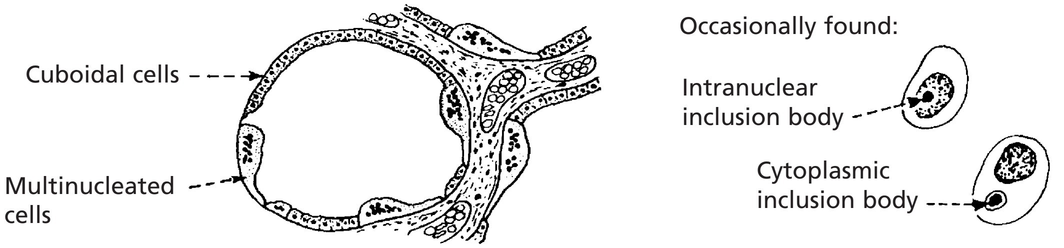


2. **Interstitial pneumonia**



3. **Reactive changes**

The lining epithelial cells of bronchioles and alveoli are stimulated by the presence of the virus.



Variations in the basic pattern occur in different infections. Confluent consolidation is often found in psittacosis and ornithosis (excreted by infected birds) and in measles giant cell pneumonia. Interstitial pneumonia is produced by cytomegalovirus and in rickettsial infections such as Q fever and 'scrub typhus'. In mycoplasma pneumonia, inflammation spreads from the bronchioles into the lung parenchyma and may become chronic with fibrosis.

PNEUMONIA – SPECIAL TYPES

ASPIRATION PNEUMONIA

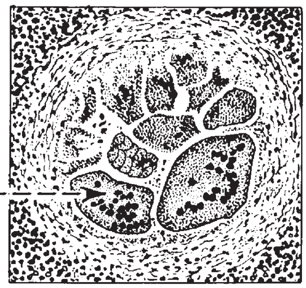
This is due to inhalation of food or infected material from the mouth or pharynx. It may occur during anaesthesia or coma or may complicate conditions associated with frequent regurgitation, e.g. oesophageal obstruction, pyloric stenosis or poor swallowing due to stroke or motor neurone disease.

In adult cases the inhalation of acid gastric contents may cause an initial shock reaction: in other cases the onset is insidious.

Possible progression is as follows:

Inhalation of foreign material ⟶ Secondary infection ⟶ Bronchopneumonia lung abscess

Histologically 'foreign material', usually vegetable matter, may be seen evoking a foreign body giant cell reaction.



Lipid pneumonia

– The exogenous form is due to long-continued inhalation of small quantities of oily material usually derived from nasal medicaments: it is often clinically silent. Oily vacuoles are seen in the lung tissue.

– The endogenous form is derived from tissue lipid debris distal to local bronchial obstruction. Foamy macrophages accumulate and the lung tissue is golden yellow in colour.

Miscellaneous pneumonias

Opportunistic infections are seen in therapeutically immunosuppressed patients and in AIDS cases.

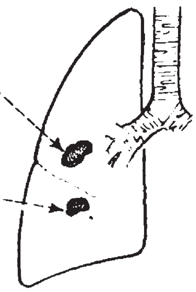
The causative agents include:

Viruses - e.g. *Cytomegalovirus*
Bacteria - e.g. *Mycobacterium avium intracellulare*
Fungi - e.g. *Pneumocystis jiroveci, Cryptococcus neoformans, Aspergillus fumigatus, Candida albicans.*

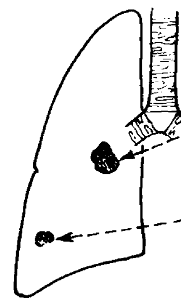
LUNG ABSCESS

This is now an uncommon condition due to prompt treatment of preceding infection. The usual causes are:

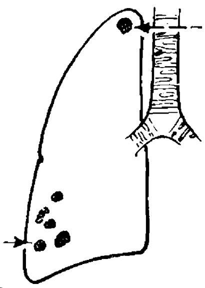
1. Inhalation of infected material from the larynx or pharynx.



2. Obstruction of a bronchus by tumour growth or foreign body. Site depends on size of bronchus affected.



3. Infection of pre-existing cavities, e.g. in tuberculosis or bronchiectasis.
4. Pneumonia. Abscess is most likely to occur in debilitated persons with bronchopneumonia.



Rarer causes of abscess are: pyaemia, trauma to lung, extension from suppuration in mediastinum, spinal column or subphrenic region, and infection with *Entamoeba histolytica*.

Sequelae of lung abscess

1. Small abscesses may heal.
2. Subpleural abscesses may extend to cause empyema.
3. Bronchopleural fistula resulting in pyopneumothorax is a further complication following on (2).
4. If a large pulmonary vessel is eroded, fatal haemorrhage can occur.
5. Rarely, blood spread leads to meningitis or cerebral abscess.

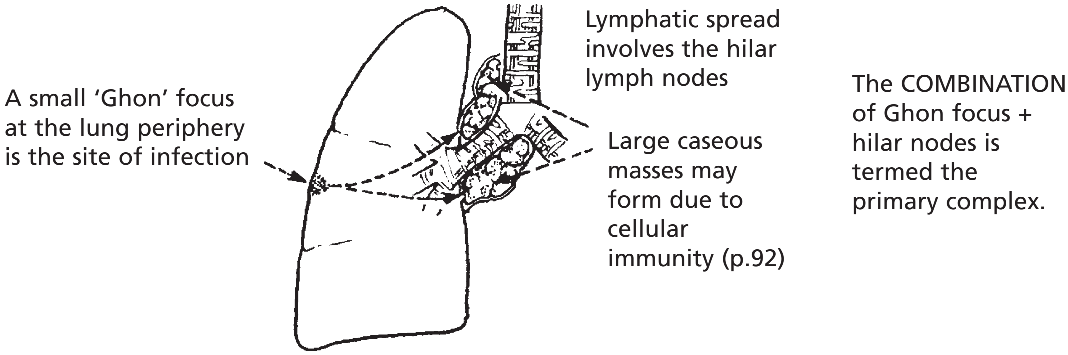
TUBERCULOSIS (TB)

The lungs are more commonly affected by TB than any other organ. The incidence of TB in developed countries is rising, partly due to AIDS. Drug resistant strains of Mycobacteria are an increasing problem.

There are 2 patterns of pulmonary tuberculosis — primary and secondary.

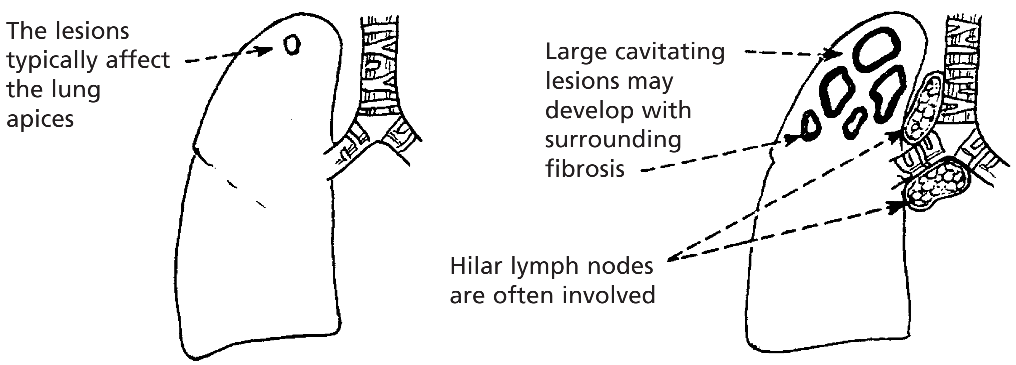
PRIMARY INFECTION
This occurs in patients, usually children, who have not been previously exposed to TB or vaccinated against it.

Infection is by inhalation.



In most patients, the lesions undergo fibrosis or calcification and heal. Spread can, however, occur.

SECONDARY INFECTION
This is a recurrence of TB in later life — either reactivation or reinfection. The patients have immunity to TB and develop a cellular response leading to CASEATION.



SPREAD OF TUBERCULOSIS

SPREAD OF TUBERCULOSIS

This is typically seen in secondary TB, but may also complicate primary infection.

The infection can spread by several pathways.

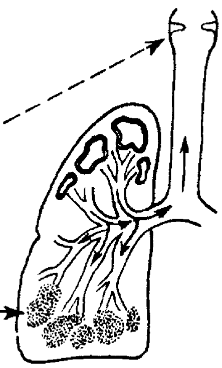
(a) **Direct spread -** e.g. to pleura and pericardium.

(b) **By the bronchi.**

Tubercle bacilli may spread to the larynx or by the bronchi to give tuberculous bronchopneumonia (‘Galloping consumption’).

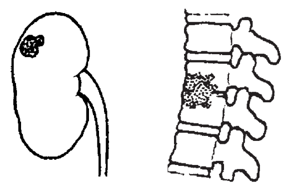
Consolidation is seen throughout large areas of lung parenchyma.

This occurs particularly in the immunosuppressed.



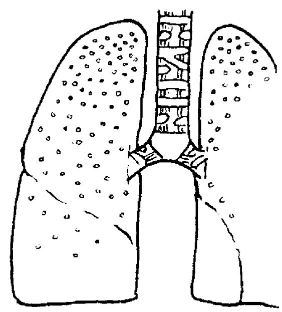
(c) By **the pulmonary veins.**

This may lead to isolated blood borne infection e.g. tuberculous meningitis (p.551), renal TB and bone TB, e.g. Pott’s disease of the spine: or to miliary spread throughout the body.



(d) **By the pulmonary arteries** (probably by lymphatics draining into the inferior vena cava).

In this, miliary spread occurs throughout the lung fields alone.



Miliary tubercles, approximately 1–2 mm, are seen throughout the lung fields.

The clinical course of tuberculosis is variable and depends on the immune status of the individual, the response of the bacteria to drugs, and intercurrent disease.

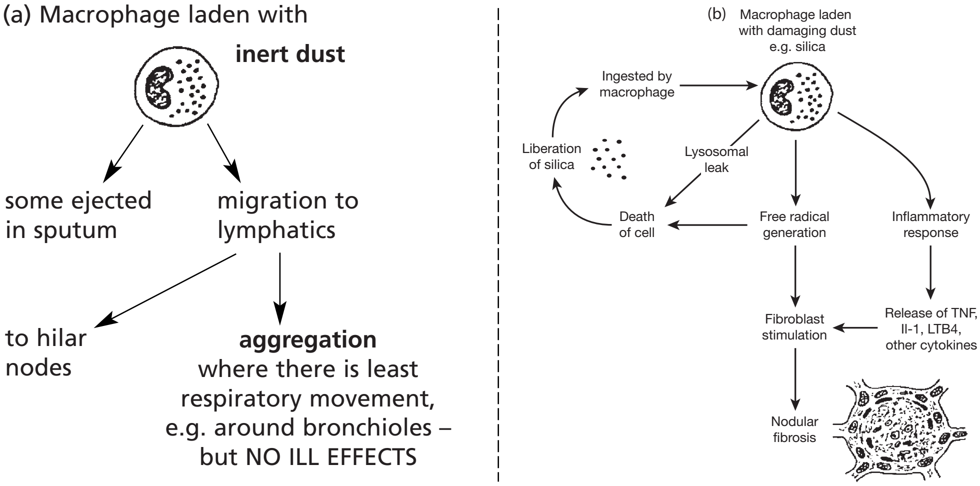
The **histological** features are as described on page 72.

PNEUMOCONIOSES (DUST DISEASES)

The reaction to inhaled dust varies very considerably. Some dusts, e.g. pure carbon, are inert: others, e.g. silicates, cause severe lung disease.

Basic Pathology

1. *Inorganic dust* particles reaching the lungs are ingested by alveolar macrophages.



2. *Organic dust* particles which cause lung disease by a different mechanism include FUNGI encountered in many occupations, e.g. farmers, malt workers, bird fanciers.

The basic pathology is a Type III hypersensitivity reaction (p. 102) and the term hypersensitivity pneumonitis (Extrinsic allergic alveolitis) is used.

Inhalation of antigen ⟶ Antigen-antibody complex ⟶ Inflammation
- Removal of antigen ⟶ Resolution
- Repeated exposure ⟶ Chronic inflammation and fibrosis

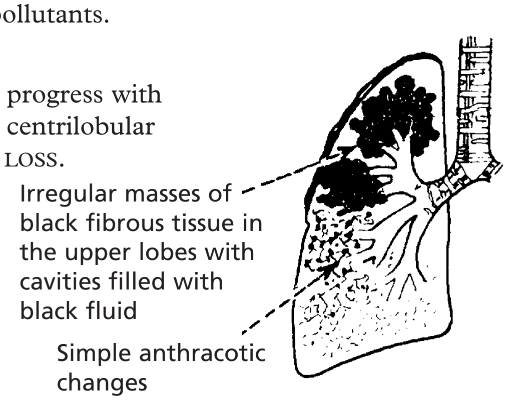
ANTHRACOSIS

Pure carbon is biologically inert and is deposited as in (a) above with no ill effects. Damage to the lung seen in coal-miners and in populations exposed to carbon polluted atmosphere is potentiated by the content of silicates and other pollutants.

Coal-miner's Pneumoconiosis

1. Simple aggregation of coal dust particles may progress with the formation of small dust nodules and mild centrilobular emphysema (p.260) with MINIMAL FUNCTION LOSS.
2. In a few cases, Progressive Massive Fibrosis supervenes with SEVERE DISABILITY.

The cause is unknown, theories include tuberculous infection as an initiator dust dose and composition, genetic factors and deviant immune responses.



PNEUMOCONIOSES (DUST DISEASES)

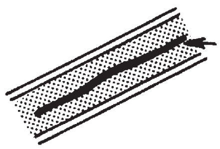
The severe diseases caused by inorganic dust inhalation, usually occupationally, are described.

1. **Silicosis** – stone workers, sandblasters, miners.
2. **Asbestosis** – shipbuilding, insulation, electrical work.

The damage caused depends on:

(a) The type of dust e.g. soluble/insoluble.

(b) The shape of the particle, e.g.

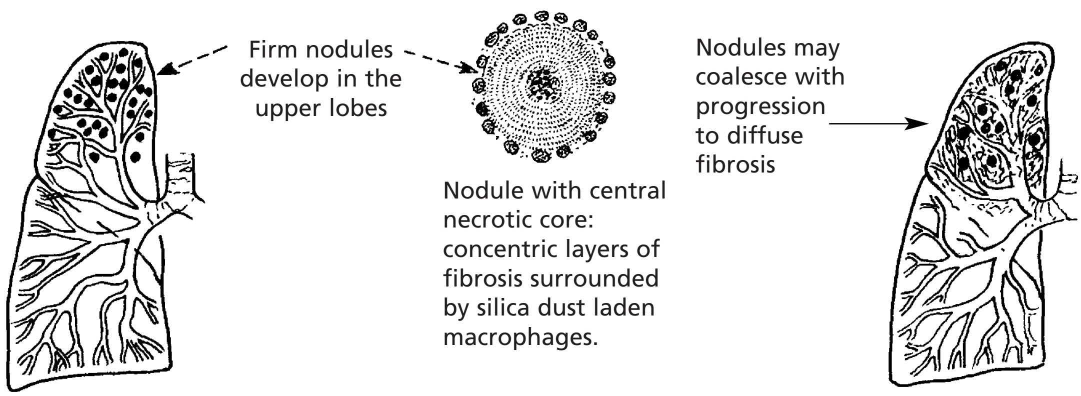


(c) The size of the particle — particles longer than 5 μm are likely to be trapped in the nose and large airways.

(d) The amount of exposure — large amounts overwhelm the defence mechanisms (especially lung macrophages).

SILICOSIS

The lung lesions are slowly progressive over many years. Silicates are particularly damaging to lung macrophages (see p. 272).



Patients develop increasing breathlessness and may die of respiratory failure and cor pulmonale.

The silicotic lung is particularly susceptible to **tuberculosis** (which may be due to the effects of silica on pulmonary macrophages). Historically, this was an important cause of death.

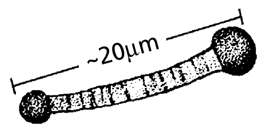
ASBESTOSIS

Asbestos is the generic name for a group of fibrous silicates widely used in heavy industry for insulation (particularly in shipbuilding).

There are two distinct forms of asbestos – serpentine (curly and flexible) and amphibole (straight and stiff). Amphibole fibres (crocidolite and amosite) are more pathogenic than serpentine fibres (principally chrysotile).

Asbestosis results from chronic exposure.





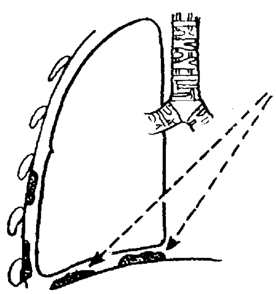
Other important complications are:

1. **Lung cancer**

Asbestos workers have an increased risk of lung cancer, especially if they also smoke. Risk of cancer = risk due to smoking × risk due to asbestos.

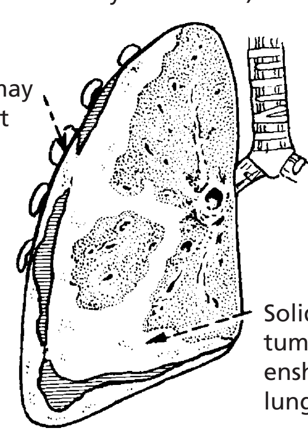
2. **Pleural pathology**

(a) **Pleural plaques** – these are the most common manifestation of asbestos exposure.



(b) **Mesothelioma** (Malignant tumour of the pleura.)

This can occur up to 40 years after a brief exposure to asbestos (particularly crocidolite).



Note: There are usually significantly fewer asbestos fibres/bodies in mesothelioma than in asbestosis.

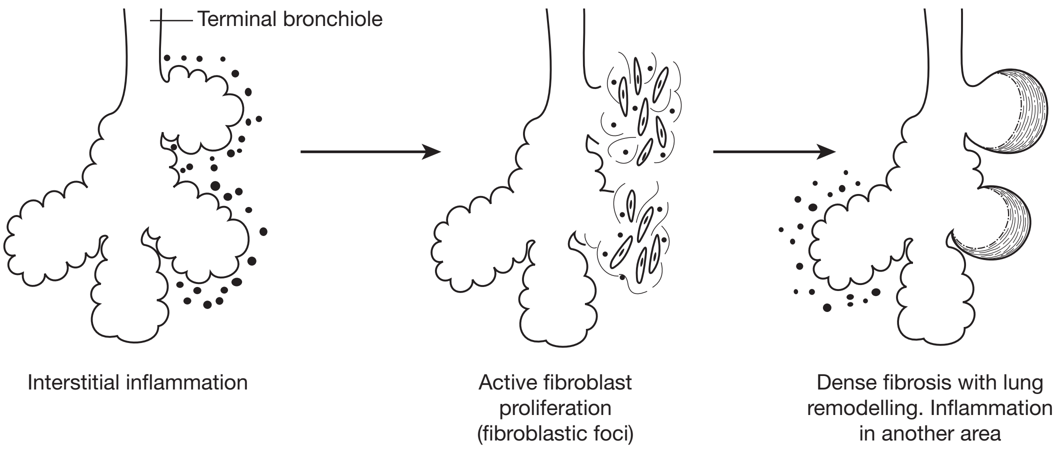
Note: Mesothelioma may also affect the pericardium and peritoneum.

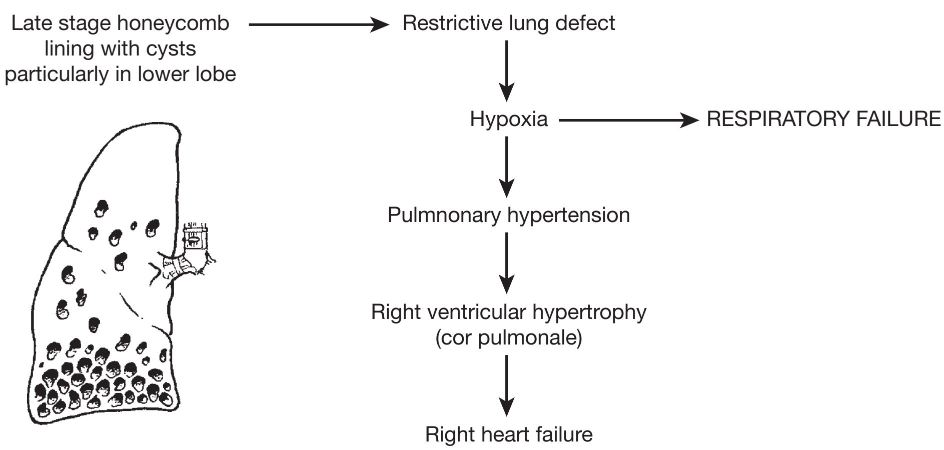
DIFFUSE PARENCHYMAL LUNG DISEASE

DIFFUSE PARENCHYMAL LUNG DISEASE

This encompasses a group of conditions in which the lung is altered by a combination of interstitial inflammation and fibrosis. Several histological patterns are recognised but it is thought that regardless of the type the earliest manifestation is alveolitis and that this accumulation of leucocytes results in release of mediators that can injure parenchymal cells and stimulate fibrosis.

1. *Usual Interstitial Pneumonia (UIP) (idiopathic pulmonary fibrosis)*
   UIP is considered to be the caused by repeated cycles of alveolitis. Healing after each cycle gives rise to fibroblastic proliferation known as fibroblastic foci such that as the disease progresses the fibrosis is a different stages (temporal heterogeneity).

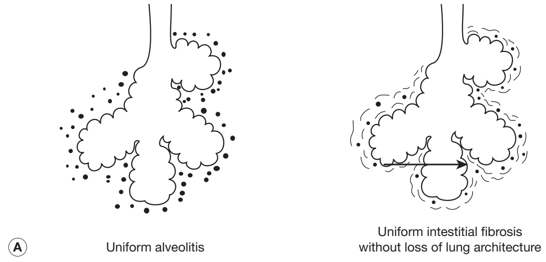




Infection is a common terminal event, and there is an increased risk of lung cancer.

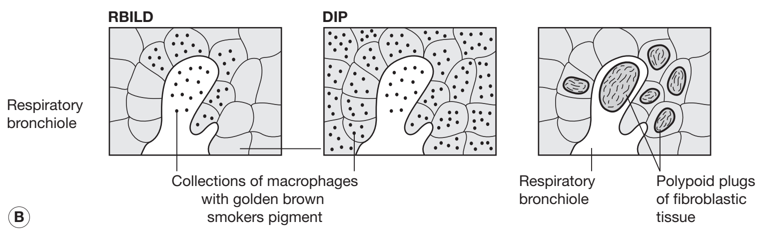
DIFFUSE PARENCHYMAL LUNG DISEASE

2. *Non-Specific Interstitial Pneumonia (NSIP)*
   This form of fibrosis has a much better prognosis than UIP and is usually steroid responsive. The lung is uniformly affected by interstitial fibrosis and inflammation of variable severity. Fibroblastic foci are abscent and progression to honeycombing is rare. This pattern is commonly seen in association with connective tissue diseases.



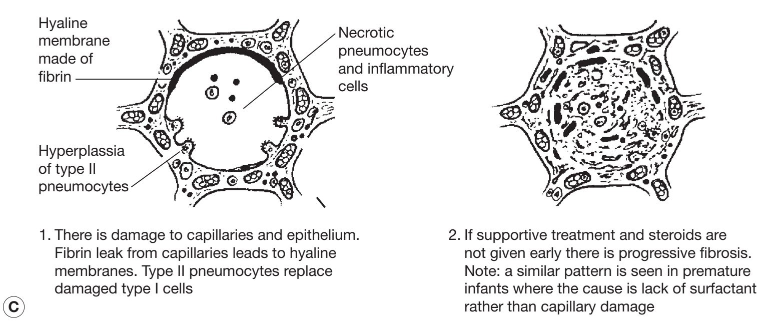
3. *Desquamative Interstitial Pneumonia (DIP) and Respiratory Bronchiolitis Interstitial Lung Disease (RBILD)*
   These patterns are both seen almost exclusively in cigarette smokers. In RBILD macrophages accumulate in a patchy distribution around respiratory bronchioles. In DIP there is diffuse distribution of macrophages.

4. *Cryptogenic Organising Pneumonia* (Bronchiolitis obliterans organising pneumonia). This characterised by a patchy distribution of polypoid plugs of fibroblastic tissue in alveoli, alveolar ducts and sometime bronchioles. A similar pattern may be seen with certain infections, drugs or connective tissue diseases.



DIFFUSE ALVEOLAR DAMAGE

This is the pathological correlate of Adult Respiratory Distress Syndrome. It may be caused by sepsis, gastric aspiration, trauma and inhaled toxins. It may also be idiopathic – Acute Interstitial Pneumonia (AIP; synonymous with Hamman–Rich Syndrome).



LUNG CANCER

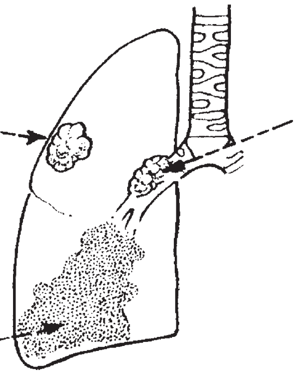
Lung cancer (carcinoma of the bronchus) is the commonest form of cancer and one which is largely preventable. Approximately 35 000 patients die of lung cancer in the United Kingdom each year.

Gross Pathology

The tumour arises from the main bronchi or their large branches (central) or at the periphery of the lung (peripheral)

Most patients present with cough, haemoptysis or chest pain, but metastases may be the first sign.

The lung distal to the tumour may collapse or become consolidated (Retention pneumonia).

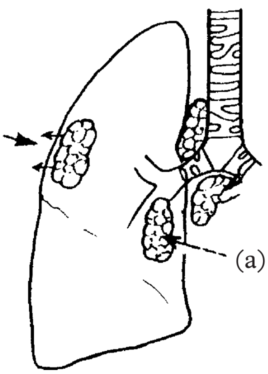


Central tumours arise from the bronchial mucosa and form a friable mass which often partly obstructs the bronchial lumen.

Tumour spread

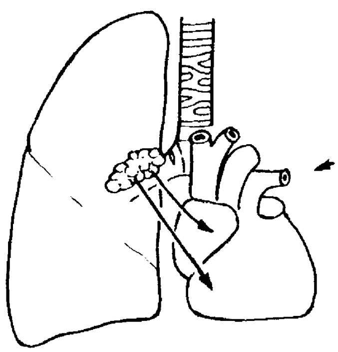
1. **LOCAL SPREAD**

(b) Pleural involvement often results in a haemorrhagic effusion.



(c) Hilar lymph nodes are often involved – with extension into mediastinal nodes.

(a) The tumour directly invades adjacent lung tissue. Invasion of a large blood vessel may lead to severe haemorrhage (Haemoptysis).

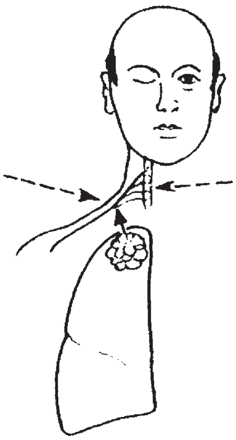


(d) Direct spread to the pericardium may cause pericardial effusion with subsequent involvement of the myocardium.

LUNG CANCER

LOCAL SPREAD *(continued)*

(e) Apical tumours (**Pancoast tumour**) can involve structures in the neck.



Involvement of the brachial plexus can give sensory and motor symptoms

Involvement of cervical sympathetic chain causes Horner's syndrome:
- Ptosis – drooping eyelid.
- Enophthalmos – sunken eye.
- Miosis – small pupil.
- Anhydrosis – loss of sweating.

(f) **Spread to the mediastinum**

(i) The superior vena cava can be obstructed – venous congestion in head and neck.

(ii) Nerves may be involved –
Recurrent laryngeal ➛ vocal cord paralysis.
Phrenic ➛ paralysis of diaphragm.

2. **DISTANT SPREAD**

Haematogenous spread is common, usually due to invasion of pulmonary veins. The common sites are: LIVER, BONE, BRAIN, ADRENAL (the last is usually asymptomatic but is found frequently at autopsy).

Lymphatic spread to cervical nodes and retrograde spread to the abdomen occurs.

NON-METASTATIC EFFECTS
These include:

1. ACTH secretion ➛ Adrenal hyperplasia ➛ Raised blood cortisol ➛ Cushing's syndrome.
2. ADH secretion ➛ Retention of water ➛ Dilutional hyponatraemia
3. Parathyroid hormone related peptide (PTHrP) secretion ➛ Hypercalcaemia (p.25).

Other syndromes include: encephalopathy, cerebellar degeneration, neuropathy, myopathy, Eaton Lambert myasthenia-like syndrome, etc.

LUNG CANCER

HISTOLOGICAL TYPES

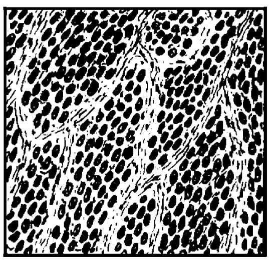
Four main types are recognised

1. Small cell	20%.	The proportions vary between series.
2. Squamous carcinoma	30%.	
3. Adenocarcinoma	40%.	
4. Large cell carcinoma	10%.	

The separation of small cell carcinoma from non-small cell variants is extremely important as the former tumour is treated by chemotherapy. Sub-classification of non-small cell variants is now important for certain targetted chemotherapies.

SMALL CELL LUNG CARCINOMA

This is the most aggressive form of lung cancer and metastasises early and widely. It does respond well, at least initially, to cisplatin based chemotherapy – some patients survive for up to 2 years.



Almost no cytoplasm.

Spindle-shaped dark nuclei; may appear to be rounded or oval. May be arranged in sheets, cords or small round aggregates.

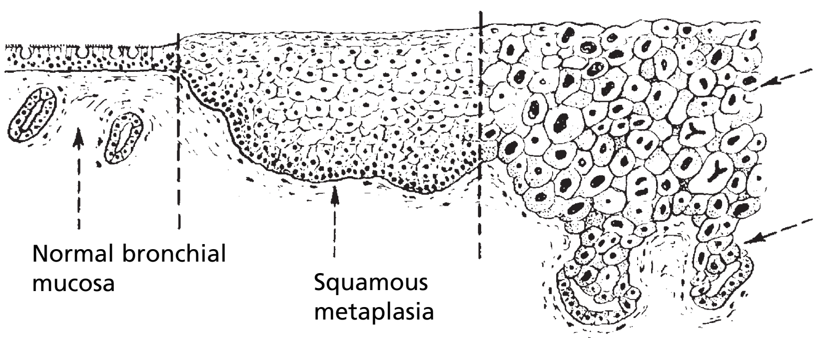


Clusters of hyperchromatic cells with nuclear moulding may be seen on sputum cytology

The tumour arises from neuro-endocrine cells and expresses markers such as NCAM-1. It is the form which most commonly has endocrine and other non-metastatic humoral effects.

SQUAMOUS CARCINOMA

These tend to arise centrally from major bronchi, within dysplastic squamous epithelium following squamous metaplasia.



Although squamous carcinoma is often slow growing, there is often extensive destruction of local tissues. The affected bronchi are often blocked, leading to retention pneumonia or collapse.

LUNG CANCER

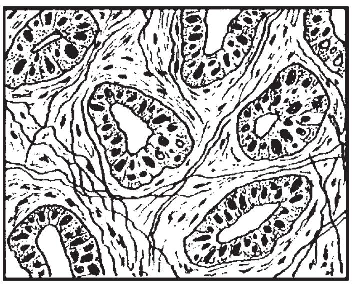
HISTOLOGICAL TYPES *(continued)*

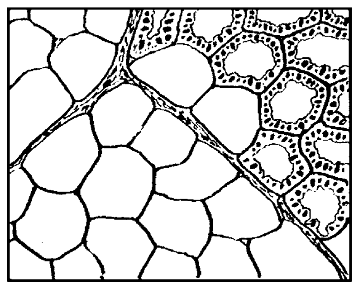
ADENOCARCINOMA
This tumour is a common tumour in women and is seen in non-smokers, but is also associated with smoking. At least two-thirds arise in the periphery of the lung, sometimes in relation to scarring. In non-smoking women, particularly of East Asian origin, there is a high incidence of epidermal growth factor receptor mutations that confer responsiveness to certain chemotherapeutic agents.

Two main patterns are seen:

(a) A well defined mass of malignant cells arranged in acini with a fibrous stroma.

(b) Growth of tumour cells along the alveolar walls (so-called 'bronchioalveolar carcinoma').





LARGE CELL CARCINOMA
As the name suggests, this tumour consists of large malignant cells without any specific differentiation. This is therefore a diagnosis of exclusion. The tumour usually arises centrally.

AETIOLOGY OF LUNG CANCER
The main factors are:

1. *Cigarette smoking* – This is by far the major cause, established by epidemiological and animal studies. Cigarette smoke contains carcinogens such as 3,4 benzpyrene and nitrosamines. Passive smoking is also significant.

2. *Industrial and atmospheric pollution* — There is a large number of pollutant industrial processes e.g. asbestos workers, miners exposed to irradiation (e.g. radon, uranium) and metal smelters (e.g. chromium and nickel).

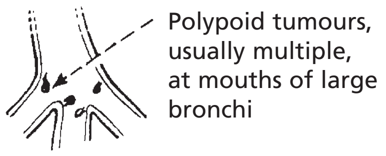
Lung cancer is more common in urban than in rural areas.

SECONDARY LUNG TUMOURS
It must always be remembered that many other cancers spread to the lungs both by blood and lymphatic routes.

OTHER TUMOURS OF THE BRONCHI AND LUNGS

Benign tumours of the bronchi and lung are unusual. There are 2 main types.

1. **SQUAMOUS PAPILLOMA**

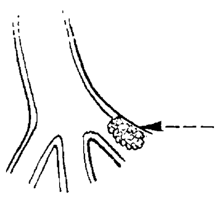


Papillomas are similar to the papillary tumours of the larynx. They occur in young people and on occasion may cause stridor due to partial bronchial obstruction. They are due to papilloma virus infection (types 6 and 11). Malignant change is exceptional.

2. **CHONDROID HAMARTOMA**

These are uncommon lesions of the lung which consist of lobules of cartilage and cleft-like spaces lined by bronchial epithelium. Their importance is that they appear as 'coin lesions' on chest X-ray and may simulate primary or secondary tumours. Current evidence suggests they are benign neoplasms rather than hamartomas.

CARCINOID TUMOURS



These tumours account for 1–2% of primary lung neoplasms. They often appear around the age of 50 years. Usually the tumour is situated in a primary bronchus or at the lung periphery. The tumour is a smooth surfaced yellow nodule.

Histologically these resemble carcinoid tumours of the appendix (see p.334). A small proportion of these tumours metastasise to regional lymph nodes – all are potentially malignant.

Central tumours tend to block the bronchus in which they arise.

Obstruction → Collapse of lung
Obstruction → Infection → Pneumonia
Infection → Bronchiectasis
Infection → Lung abscess

Atypical carcinoid tumours: This sub-group of tumours shows nuclear pleomorphism, mitotic activity and necrosis. Over half eventually metastasise.

Tumours of bronchial glands
Both benign and low grade malignant tumours of the bronchial glands are occasionally seen and show histological similarity to salivary gland tumours. These may present as obstructing lesions.

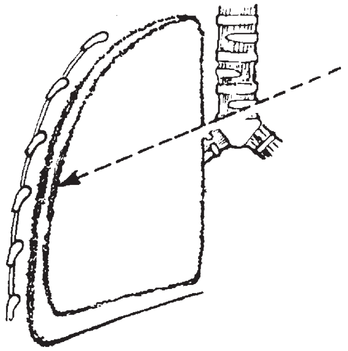
DISEASES OF THE PLEURA

INFLAMMATION (PLEURISY)

There are several causes.

(a) *Infection* – usually due to spread from pneumonia or tuberculosis.
– following penetrating injury, e.g. stab wound.
(b) *Autoimmunity* – e.g. rheumatoid arthritis, systemic lupus erythematosus.
(c) *Overlying a pulmonary infarct* (p.162).

FIBRINOUS PLEURISY



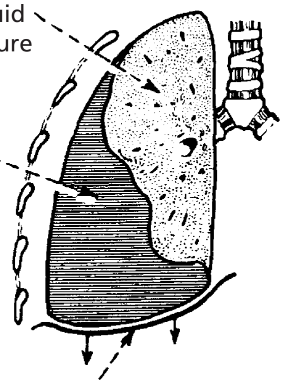
Fibrinous exudate on parietal and visceral layers → Pleural friction rub, pleuritic chest pain due to movement on respiration

The exudate is absorbed but organisation may lead to pleural adhesions.

If fluid accumulates in excess, there is a pleural effusion – pain and friction rub disappear as the inflamed layers are separated.

If infection of the pleura proceeds, an empyema (a collection of pus in the pleura) may form. This is now unusual.

PLEURAL EFFUSION



The accumulation of fluid within the pleura can be explained as a form of local oedema.

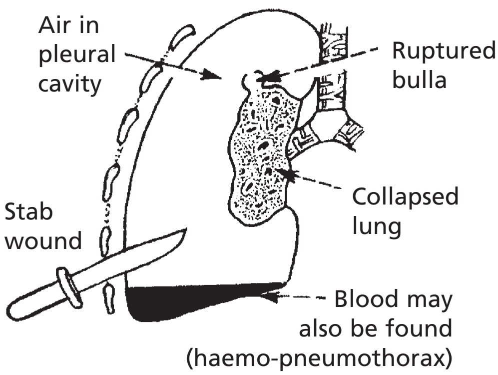
The composition of the fluid is related to the underlying cause.

TRANSUDATE	EXUDATE
e.g. in heart failure – low protein content; – few inflammatory cells.	e.g. in fibrinous pleurisy – high protein content; – numerous inflammatory cells.

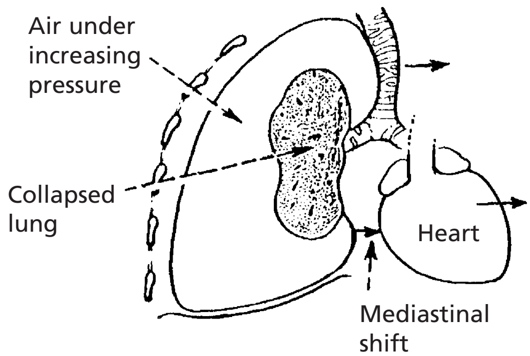
Examination of the pleural fluid may show mesothelial cells, lymphocytes, macrophages, neutrophils and sometimes tumour cells.

DISEASES OF THE PLEURA

PNEUMOTHORAX
This is the accumulation of air in the pleural space. It may follow blunt trauma or penetrating wound, e.g. stabbing. Older patients with emphysema may develop spontaneous pneumothorax. In young people this is usually due to rupture of small bullae or excessive smoking of cannabis.



In a TENSION PNEUMOTHORAX there is a valve effect – air continues to enter the pleura during inspiration but cannot exit during expiration.



Patients complain of chest pain and breathlessness.

PLEURAL MALIGNANCY

Metastatic tumours affect the pleura in 2 ways.

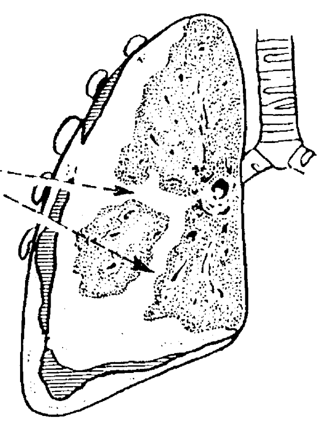
(a) By LYMPHATIC spread – with numerous small nodules, e.g. breast carcinoma.

(b) By DIRECT spread, e.g. lung cancer.

There is usually a pleural effusion in which tumour cells can be found.

Malignant Mesothelioma
This primary pleural malignancy is usually due to asbestos exposure — often many years before.

The tumour may encase the entire lung and grow into the interlobar fissures



There is often a malignant pleural effusion.

The tumour can metastasise to other sites, but most patients die due to the local respiratory effects.



Histologically, the tumour consists of either epithelial or sarcomatous tissues, or may be mixed (biphasic)

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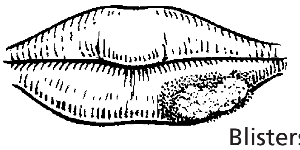
CHAPTER 9

GASTROINTESTINAL TRACT

THE MOUTH

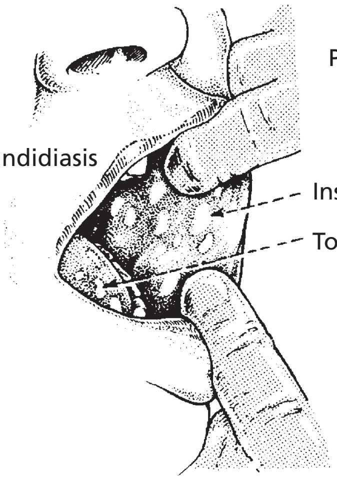
INFLAMMATION
A wide variety of inflammatory conditions is seen.

VIRAL INFECTIONS
Herpes simplex virus (usually type I) infects the mouth in young children – this is often asymptomatic but in 10–20% of cases numerous vesicles and ulcers are seen. The virus can become latent in the trigeminal ganglion and repeated 'cold sores' occur on the lip in later life.



Coxsackie viruses can cause oral blistering (e.g. herpangina; hand, foot and mouth disease). Koplik's spots are a feature of *measles*.

FUNGAL INFECTION
Candida albicans is an oral commensal in 40% of the population.



Clinical infection is seen in infants, in patients on broad spectrum antibiotics, steroid or cytotoxic therapy and also in the immunosuppressed and diabetics. Extensive oral candida is common in patients with AIDS.

BACTERIAL INFECTIONS

Syphilis, now uncommon in the West, can involve the mouth as a primary chancre, irregular lines of ulceration – snail track ulcers of the secondary stage, and as small gummas (tertiary).

Oral tuberculosis, usually due to coughed up bacilli from pulmonary TB, is now very uncommon. Ulcers may occur on the tongue.

Aphthous ulcers
Around 30% of the population are troubled by these painful, usually small, ulcers on the cheek, tongue and gums. The aetiology is unknown; in some individuals they are provoked by stress or local trauma.

Dermatoses e.g. lichen planus – can affect the oral mucosa.

ORAL CANCER

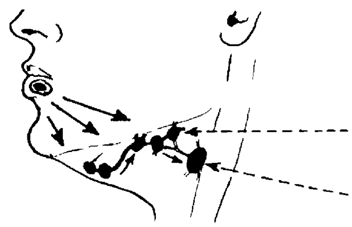
Oral cancer accounts for 2% of cancers in the United Kingdom. There is wide geographical variation – commoner in S. East Asia. Males are at least twice as commonly affected as women – it is a disease of the elderly.

Aetiology
The major causes are:

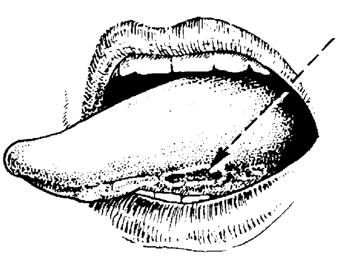
1. Tobacco – especially pipe and cigar smoking. Chewing tobacco, sometimes mixed with betel nuts (in Eastern countries) is also implicated.
2. Alcohol, especially spirits.
3. Exposure to ultra-violet light (cancer of the lip).
4. Human papilloma virus (type 16) may be involved.

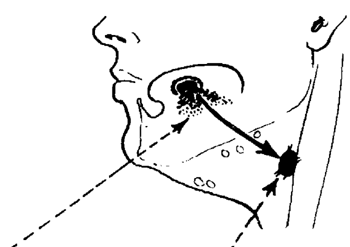
Pathology
Almost all cases are **squamous cell carcinomas**. The lip, tongue, floor of mouth and tonsil are affected in that order of frequency.





Tongue/Floor of mouth
Carcinoma of the tongue and other sites within the mouth is a more aggressive growth than tumours of the lips. Starting as a nodule in the buccal sulcus adjacent to the tongue, it breaks down to form an irregular ulcer with ragged edges.

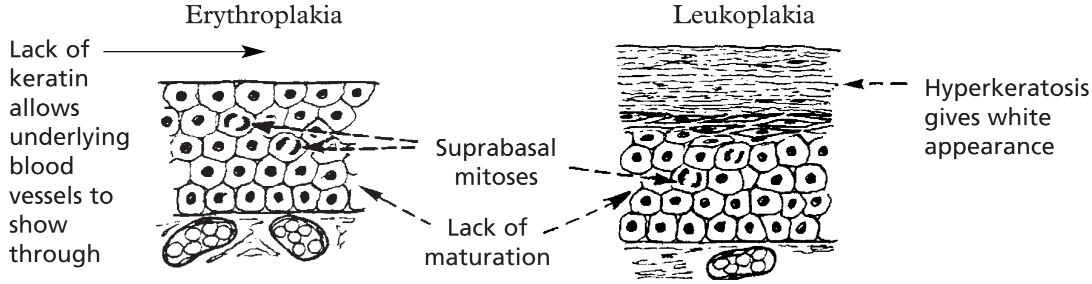




MOUTH

ERYTHROPLAKIA and LEUKOPLAKIA

These terms describe velvety red patches and white patches in the oral mucosa. These are important because they may represent dysplasia of the squamous epithelium and may lead to squamous cancer.



Not all examples of leukoplakia are premalignant and may also be due to:

- – chronic irritation (e.g. dentures)
- – pipe smoking
- – Candida.

A distinctive form – ‘hairy leukoplakia’ – occurs on the lateral border of the tongue in patients with HIV/AIDS. It is due to Epstein–Barr virus infection, often with superimposed candida.

Pigmentations

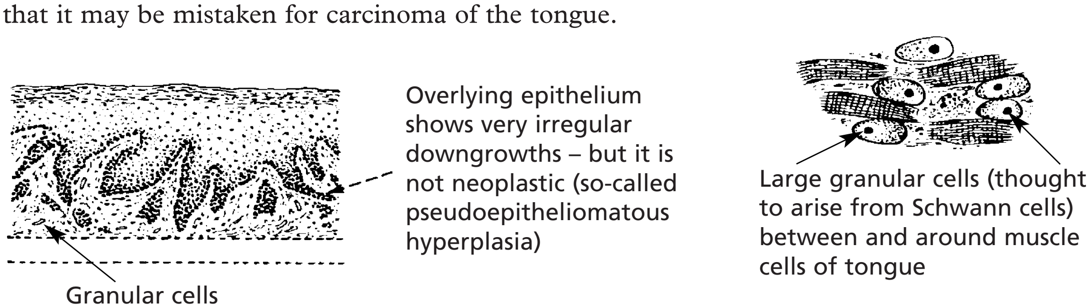
Melanotic pigmentation of the mouth is seen in Addison’s disease, haemochromatosis and the Peutz–Jeghers syndrome.

Benign Tumours

A variety of benign tumours are seen, e.g. squamous papillomas and haemangiomas (often on the lips or tongue).

Granular cell tumour

This is a rare tumour and its importance lies in the fact that it may be mistaken for carcinoma of the tongue.



Note: Epulis is a clinical term applied to swellings at the gum margin. Most of them are granulomas associated with chronic gingivitis. A few are true neoplasms.

DENTAL CARIES AND PERIODONTAL DISEASE

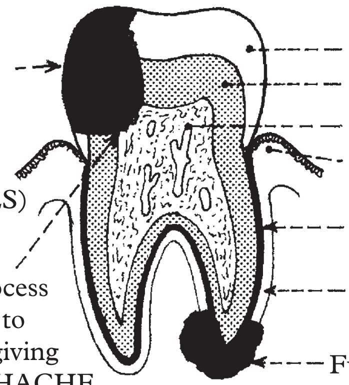
These two very common processes are primarily of importance to dentists but an understanding is also valuable for doctors.

DENTAL CARIES

This is the commonest disease of teeth.

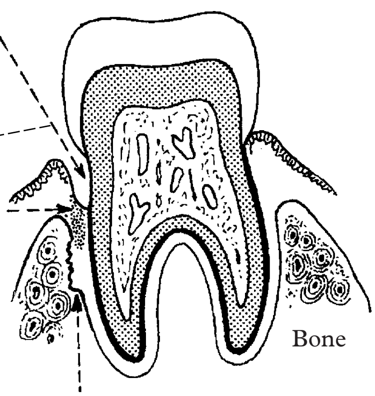
Poor oral hygiene + high sugar intake lead to formation of plaque.

Plaque includes masses of bacteria, e.g. *Streptococcus mutans* + sugar } Lactic acid and proteolytic enzymes → Remove calcified parts of tooth (CARIES)



PERIODONTAL DISEASE

This is the major cause of tooth loss in middle age. It is essentially due to gingivitis.

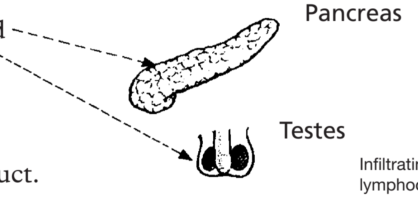


DISEASES OF THE SALIVARY GLANDS

INFLAMMATION

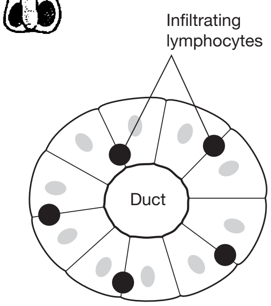
The commonest acute inflammation is due to the mumps virus, which produces acute swelling, particularly of the parotid glands, with oedema and mononuclear infiltration of the interstitial tissue.

The testes and pancreas may also be inflamed and atrophy may follow.



Bacterial infection of these glands is uncommon and may occur during a prolonged illness, particularly if a calculus has formed in a duct.

Chronic inflammation is rare. It may occur in sarcoidosis. The parotid gland becomes swollen and there may be an accompanying irido-cyclitis. This has given rise to the term ‘uveo-parotid fever’. The parotid gland shows a chronic inflammatory reaction with granulomas typical of sarcoidosis.



Sjögren’s syndrome

In this auto-immune condition there is destruction of the salivary, lacrimal and conjunctival glands by an infiltrate of lymphocytes (so-called lympho-epithelial lesions) and plasma cells. The duct epithelia often undergo reactive hyperplasia. It results in dryness of the mouth, caries due to lack of saliva, and ulceration of the conjunctiva caused by lack of secretion from the lacrimal and conjunctival glands. This is often associated with rheumatoid disease.

There is an increased risk of B cell lymphoma (p. 431).

Calculi

Stones can form in the submandibular or, less often, the parotid duct. Blockage leads to episodes of swelling after food and eventually to atrophy of the gland. Acute inflammation may be superimposed.

SALIVARY GLAND TUMOURS

The majority (80%) of tumours arise in the parotid gland and are usually benign.

The remainder occur in the submandibular and minor salivary glands where 30–40% are malignant.

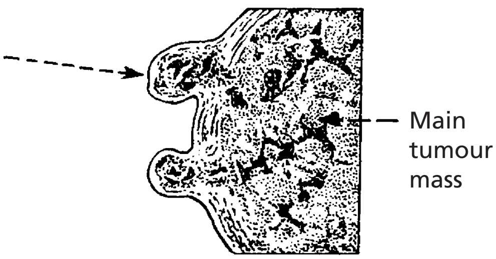
SALIVARY GLANDS – BENIGN TUMOURS

PLEOMORPHIC ADENOMA

This is the commonest tumour of the salivary glands and most often occurs in the parotid. The term 'pleomorphic' applies not to the nuclei of the cells but to the different types of tissue found. These are derived from the epithelial and myoepithelial cells.

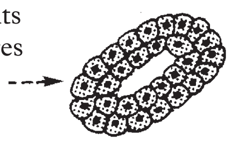
The tumour is lobulated and encapsulated but there are frequently small lobules which extend into the adjacent tissue.

If the tumour is 'shelled out' these lobules are left behind and cause local recurrence. For this reason superficial parotidectomy is usually performed, ensuring complete removal of the tumour.



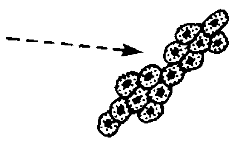
HISTOLOGY

The **epithelial** elements form duct-like structures often with 2 cell layers



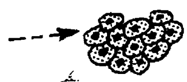
or

trabeculae



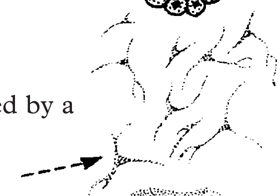
(Squamous differentiation may be seen)

The **myoepithelial** elements are seen as cellular clumps

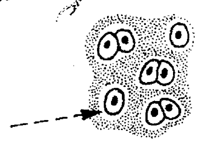


or

may be separated by a myxoid ground substance



Cartilagenous metaplasia may also occur.



MALIGNANT CHANGE

Under 5% of these tumours become malignant, often after many years. Most of these are adenocarcinomas with a poor prognosis.

WARTHIN'S TUMOUR

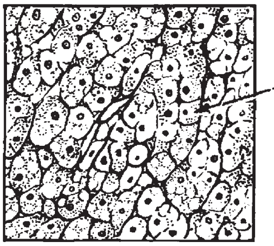
This is a benign lesion, mainly in the parotid of elderly men. It consists of tall epithelial cells with eosinophilic cytoplasm (oncocytes) and a reactive lymphoid infiltrate.

SALIVARY GLANDS – CARCINOMAS

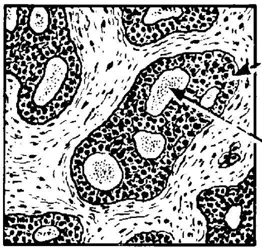
Almost all malignant tumours of the salivary glands are adenocarcinomas. They affect major and minor glands and arise de novo or from pre-existing pleomorphic adenoma. The prognosis is variable.

Three unusual subtypes are worth noting.

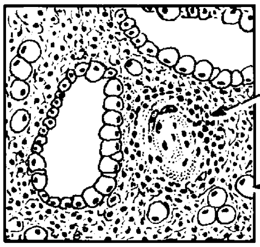
1. **Acinic cell carcinoma**
   Approximately 1/4 of all malignant parotid tumours are of this type. It grows slowly, recurs after removal and sometimes there is late spread to the regional lymph nodes and distant organs.



2. **Adenoid cystic carcinoma**
   This usually occurs in minor salivary glands. It extends by direct spread, especially along nerve sheaths, but metastases can occur to lymph nodes, lungs and bones.



3. **Muco-epidermoid carcinoma**
   The behaviour of this type varies, but all tend to recur and infiltrate locally. More aggressive tumours metastasise to the lymph nodes and may invade the blood stream. They are generally found in the major salivary glands.



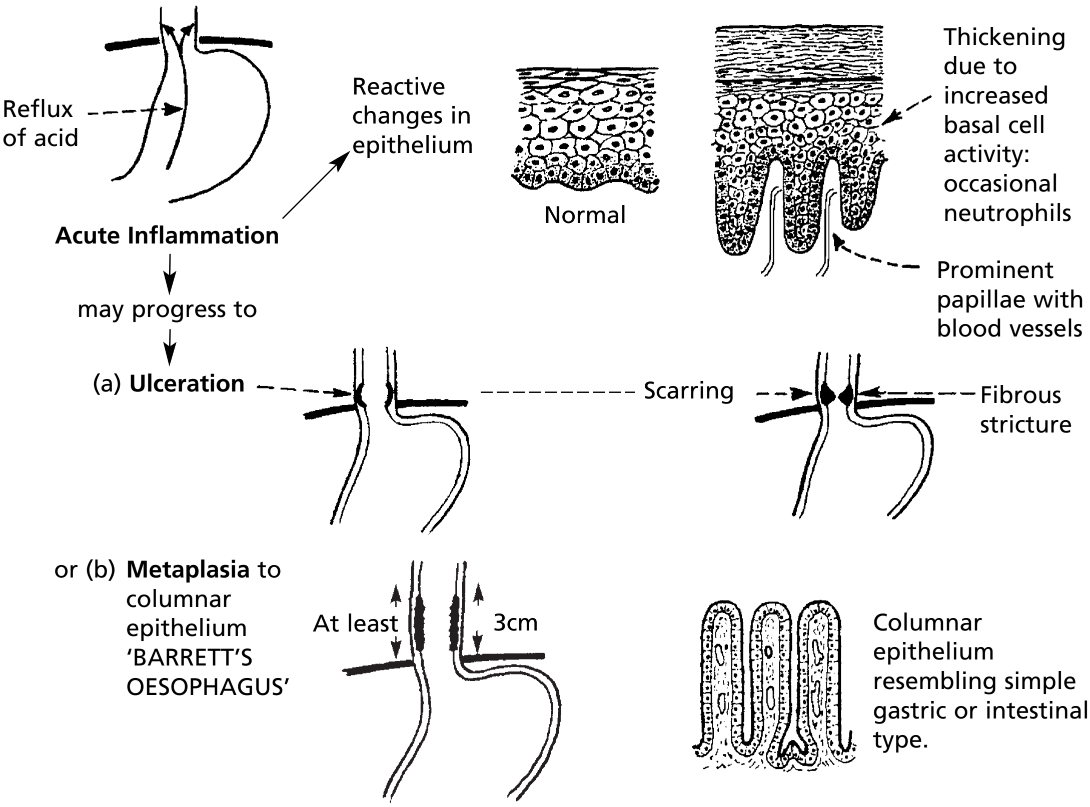
OESOPHAGUS

The oesophagus is a muscular tube 25 cm long lined by stratified squamous epithelium which is resistant to damage by heat, cold and mechanical trauma.

INFLAMMATION

Reflux oesophagitis

This is the commonest form of inflammation due to reflux of gastric acid through a relaxed lower oesophageal sphincter into the lower oesophagus, often associated with hiatus hernia.



This is an important premalignant lesion with a 30–40 fold increased risk of CANCER.

METAPLASIA ⟶ DYSPLASIA (detected by endoscopy and biopsy) ⟶ ADENOCARCINOMA

Other forms of oesophagitis

1. Eosinophilic oesophagitis. Some patients, often atopic, develop dysphagia and biopsy shows numerous eosinophils within the squamous epithelium.
2. Infection by *Herpes simplex virus*, cytomegalovirus and *Candida albicans* occurs particularly in the immunosuppressed and AIDS.
3. Ingestion of drugs, e.g. non-steroidal anti-inflammatory drugs, may cause ulceration of the distal oesophagus.

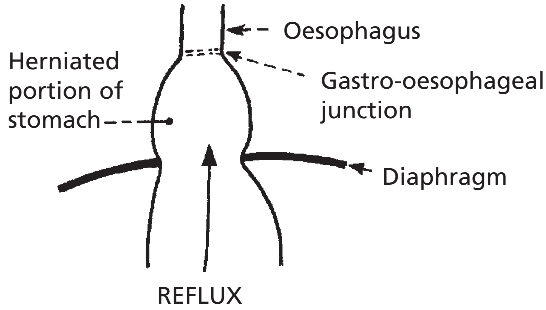
OESOPHAGUS

HIATUS HERNIA

In hiatus hernia part of the stomach herniates into the thorax. This is common, particularly in the elderly, though often asymptomatic. Two forms are seen:

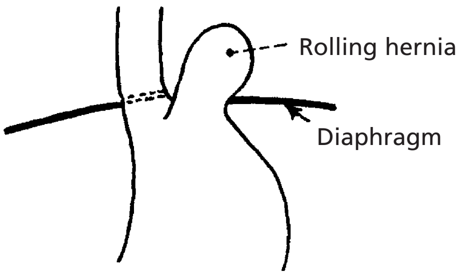
1. **Sliding hernia**

   – the distal oesophagus and proximal stomach slide proximally so the latter lies in the thorax. Most cases are of this type.



2. **Rolling hernia**

   – a loop of stomach rolls upwards and passes through the diaphragm alongside the oesophagogastric junction. Since the junction is preserved reflux is unusual.

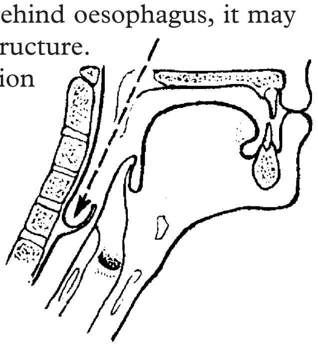


DIVERTICULA

These are relatively rare and are of 2 varieties.

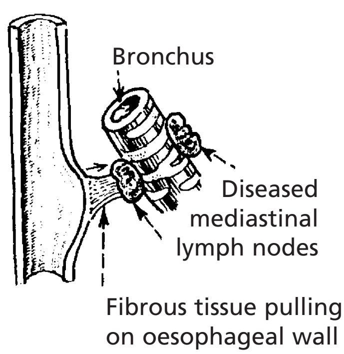
1. **Pulsion type**

Involves pharynx (pharyngeal pouch). Sac is distended during swallowing of food. By pushing down behind oesophagus, it may compress this structure. Abnormal function of the upper oesophageal sphincter is an aetiological factor.



2. **Traction type**

This is due to traction of fibrous tissue produced by mediastinal inflammation, e.g. tuberculosis of lymph nodes.



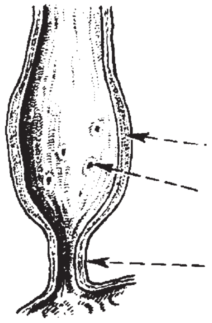
Rarely, there may be a congenital diverticulum at the level of the bifurcation of the trachea.

OESOPHAGUS

Obstruction usually leads to dysphagia – difficulty in swallowing. The causes include:

Strictures of the oesophageal wall due to:
– inflammation caused by acid reflux.
– carcinoma.
– historically mucosal webs at the upper end were a feature of the Plummer–Vinson syndrome in chronic untreated iron deficiency anaemia.

Achalasia of the oesophagus develops in young adults and may cause severe obstruction.



It is due to a conduction failure in the peristaltic mechanism preventing relaxation of the cardiac sphincter. Reduced numbers of ganglion cells are found in the myenteric plexus.

Above the obstruction the oesophagus is dilated, the muscle is hypertrophied and the mucosa may be ulcerated.

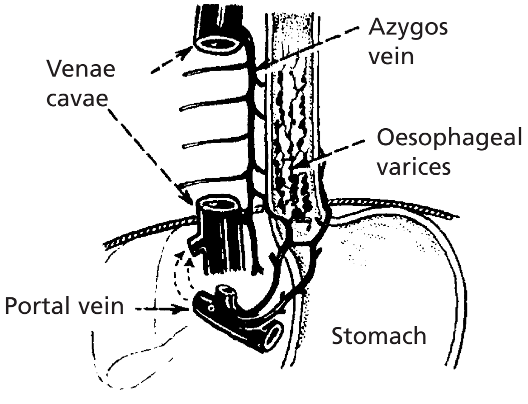
Narrowing occurs at the lower end.

(In South American trypanosomiasis the myenteric plexus may be destroyed (CHAGAS DISEASE) and long-standing diabetic autonomic neuropathy may cause a similar problem.)

In **Systemic sclerosis**, replacement of muscle by fibrous tissue converts the oesophagus into a rigid tube.

OESOPHAGEAL VARICES

These dilated veins occur secondarily to portal hypertension caused mainly by cirrhosis of the liver (see p.350).



Fibrosis in the liver obstructs the flow of blood from the gastrointestinal tract. Anastomotic channels connecting the portal and systemic venous systems open up and become distended. The most important are the oesophageal tributaries of the azygos vein which connect through the diaphragm with the portal system. They become varicose, and are easily traumatised by the passage of food, leading to haemorrhage which can be severe.

Spontaneous rupture of the oesophagus is rare. Mucosal tears causing haemorrhage may occur (Mallory–Weiss syndrome).

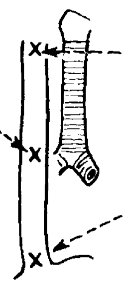
Congenital abnormalities include stenosis and atresia with fistula formation.

OESOPHAGUS – TUMOURS

Benign tumours of the oesophagus are rare. They are almost always of connective tissue origin (usually leiomyomas) and form polyps within the lumen, causing obstruction.

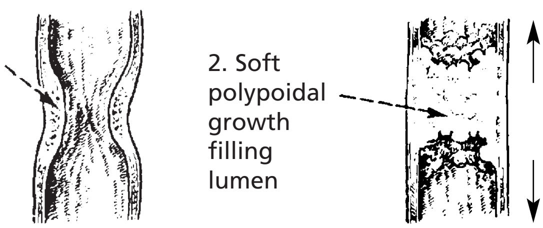
Carcinoma

Carcinoma of the oesophagus occurs in two main forms:



The disease is more common in men by at least 4 to 1.

The tumours may narrow the lumen or cause a polypoid mass



Spread

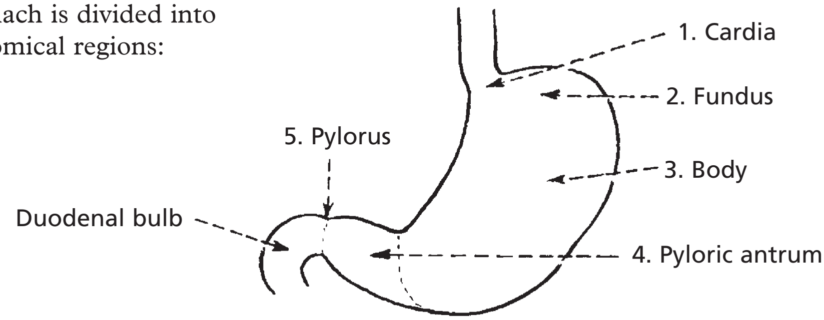
Middle third tumours may involve the trachea with fistula formation leading to aspiration pneumonia. Tumours of the lower third may invade the mediastinum. Lymph node involvement is common and blood borne metastases to liver occur late.

Aetiology

There is geographical variation, tumours being common in China and Africa. Smoking and diet, including alcohol consumption, are important in squamous carcinoma. Post-cricoid carcinoma in women is a rare late complication of the dysphagia complicating iron deficiency anaemia. Adenocarcinoma is largely due to Barrett's oesophagus and reflux.

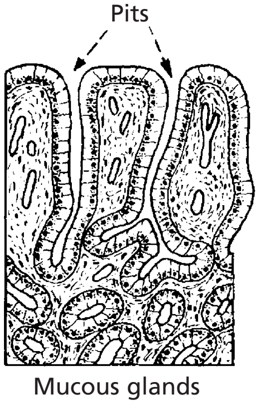
STOMACH

The stomach is divided into five anatomical regions:

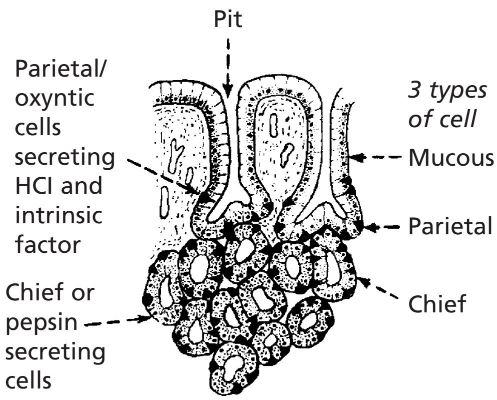


Three forms of mucosa are seen:

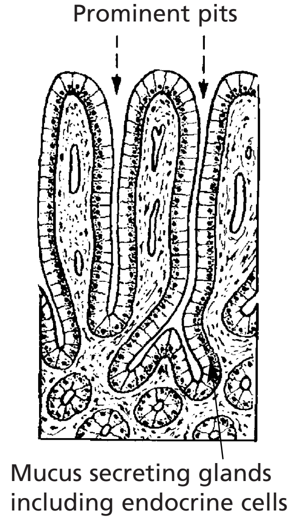
1. **Cardiac**



2. **Body and Fundus**
This is the main specialised secreting area.



3. **Antrum and Pylorus**

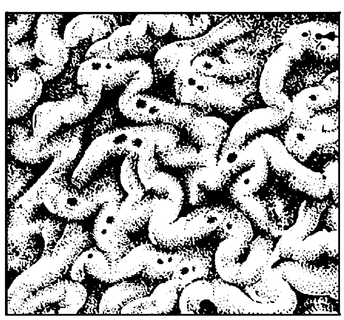


ACUTE GASTRITIS

Mild acute gastritis with neutrophils in the mucosa may be caused by alcohol and non-steroidal anti-inflammatory drugs (NSAIDs), and are seldom biopsied. Acute haemorrhagic or erosive gastritis is a more severe form, also associated with aspirin and NSAIDs, and is also a complication of shock.

Tiny ulcers affect all parts of the stomach, occuring on the apex of mucosal folds, and can heal rapidly.

Naked eye appearance



GASTRITIS

ACUTE INFLAMMATION

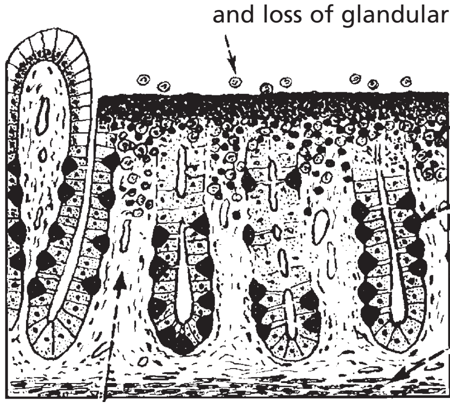
Mild acute gastritis is an acute inflammation with neutrophil reaction in the superficial layers of the mucosa. Pain and sickness have a multitude of causes varying from hot fluids, alcohol and aspirin which act as direct irritants, to infections such as childhood fevers, viral infections and bacterial food poisoning.

A more acute form, known as acute haemorrhagic or erosive gastritis, is associated with ingestion of irritant drugs, particularly aspirin and NSAIDs and is also a complication of shock states.

Haemorrhagic erosions
These are tiny ulcers, a few millimetres in diameter, which are formed by the digestion of the mucous membrane overlying small haemorrhages. They are usually multiple and affect all parts of the stomach. They occur mostly on the apex of mucosal folds and involve only the mucosa.

Note that the changes are superficial so that restoration to normal can occur very quickly occur.

Stress ulcers
Occasionally, particularly in severe shock, there is deeper acute ulceration with considerable haemorrhage and even perforation.



CHRONIC GASTRITIS

There are 3 main causes of chronic gastritis:
- *helicobacter pylori*
- chemical
- autoimmune.

1. ***Helicobacter pylori*** **ASSOCIATED CHRONIC GASTRITIS**

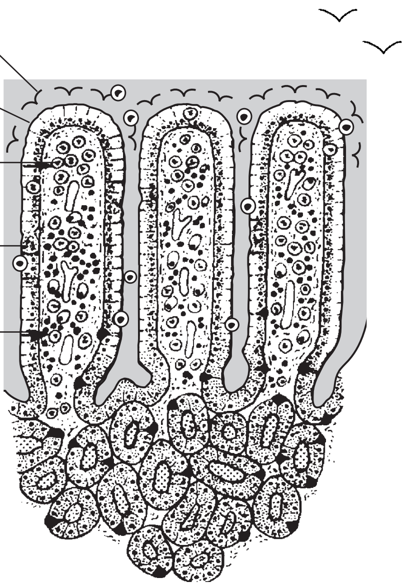
Prevalence: 80% of chronic gastritis cases are of this type. The organism has a world wide distribution. In Western countries the prevalence of *Helicobacter* is over 30% by 30 years of age. In developing countries it is even higher.

Aetiology: *Helicobacter pylori* is a Gram-negative spiral bacterium which is specifically adapted to colonise the gastric mucosa.

Site affected: The antrum and pyloric canal particularly.

Morphological changes are of mucosal inflammation.

GASTRITIS



Complications:

(a) GASTRIC and DUODENAL ulcer (see p.303).
(b) Progression to CARCINOMA, often preceded by INTESTINAL METAPLASIA.
(c) Association with LYMPHOMAS.

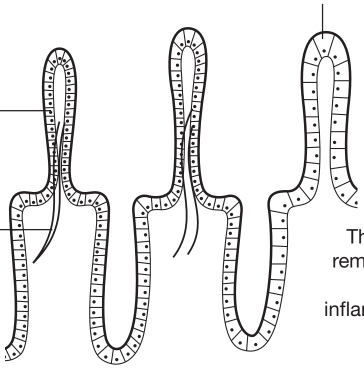
2. **CHEMICAL (REFLUX) GASTRITIS**

Prevalence: this is the second commonest cause of chronic gastritis, accounting for approximately 10% of cases.

Aetiology: due to reflux of bile from duodenum, and to drugs.

Site affected: antrum and pylorus.

Morphology: there is foveolar hyperplasia and oedema with little inflammation.



GASTRITIS

3. **AUTO-IMMUNE ASSOCIATED GASTRITIS**

Prevalence: 5% of chronic gastritis cases are of this type.

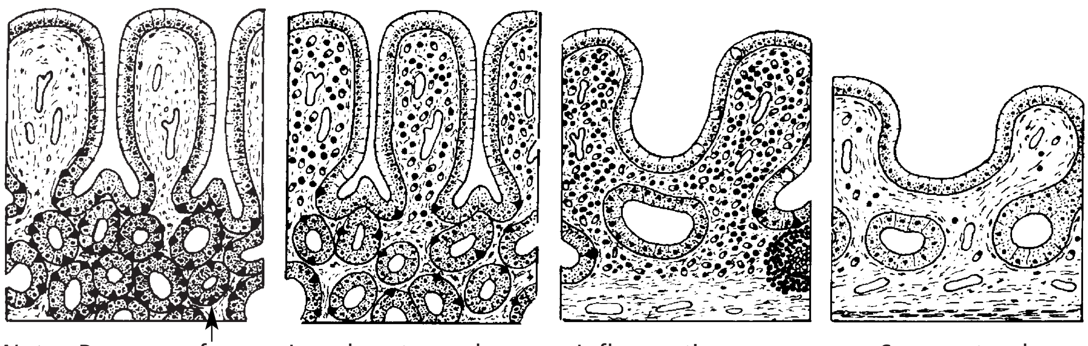
Aetiology:

(a) Presence of antibodies to parietal cells and intrinsic factor.
(b) Associated with other auto-immune disorders, e.g. thyroiditis.

Sites affected: The fundus and body predominantly.

Morphological changes are progressive over several years with gradual thinning of the mucosa.

Normal — **Early** — **Moderate** — **Final stage (severe)**



Note: Presence of specialised parietal cells. — Lymphocytes and plasma cells in lamina propria: less numerous parietal cells. — Inflammation more severe: virtually complete loss of parietal cells. — Severe atrophy. Mucous glands only remaining.

Complications:

(a) Loss of parietal cells → Achlorhydria; → Absence of intrinsic factor → Pernicious anaemia (see p.389)

(b) There is an association with the development of GASTRIC CARCINOMA often preceded by INTESTINAL METAPLASIA.

OTHER FORMS of GASTRITIS

These include eosinophilic gastritis associated with food allergy, collagen diseases and parasites.

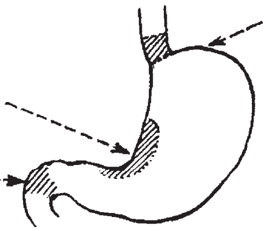
Granulomatous gastritis has many causes including Crohn’s disease, TB and sarcoidosis.

Lymphocytic gastritis shows an increase in intraepithelial lymphocytes and is often associated with coeliac disease (p. 307).

PEPTIC ULCERATION

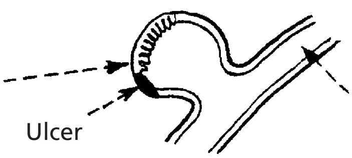
Peptic ulcers occur when acid-containing gastric juices breach the mucosa of the gut.

Chronic peptic ulcers are found in 3 main sites.



1. The first part of the duodenum. The incidence has fallen in recent years.
2. Gastric ulcers usually affect the antrum on the lesser curve.
3. Reflux of acid may lead to oesophageal ulcers.

Occasionally a peptic ulcer arises at a site of heterotopic gastric mucosa, e.g. Meckel's diverticulum.



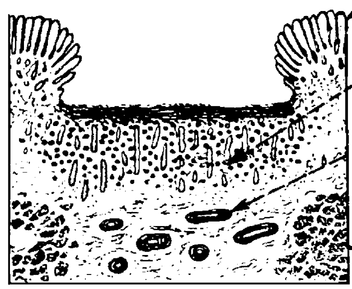
Peptic ulcers are usually solitary, but in 10% a second ulcer is found, e.g. on the opposite side of the duodenum (kissing ulcer).

A **typical chronic peptic ulcer** is a punched out oval ulcer 2–3 cm in diameter.



The surrounding mucosa often shows stellate folds due to scarring.

The ulcer bed consists of fibrin and debris.



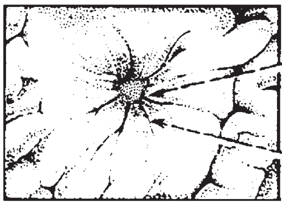
In long standing lesions fibrous tissue replaces muscle.

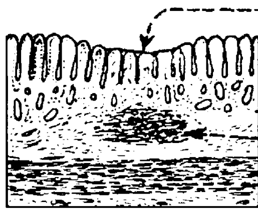
Acute gastric ulcers (often called stress ulcers) may be seen in patients with severe burns, after major trauma or with raised intracranial pressure. These may cause bleeding, but usually heal completely. Acute ulcers may also be due to treatment with NSAIDs.

PEPTIC ULCERATION

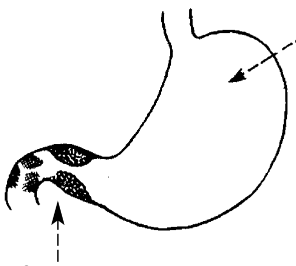
SEQUELS and COMPLICATIONS

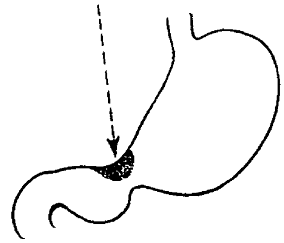
1. **Healing** is common, particularly when treated.



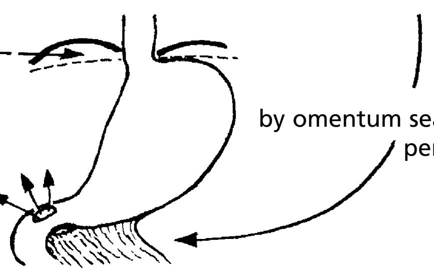


2. **Scarring** may lead to stricture formation.





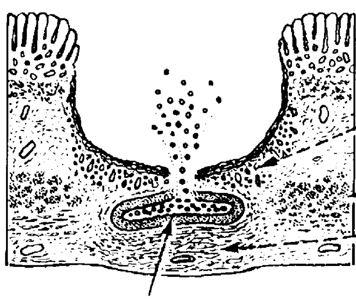
3. **Perforation** of an ulcer causes **acute peritonitis**. This may be:



4. **Haemorrhage**

Minor bleeding is common and can lead to anaemia.

Major haemorrhage can lead to haematemesis, to 'coffee ground' vomit or to melaena (tarry black stools).



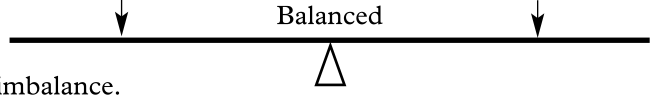
PEPTIC ULCER – AETIOLOGY

Normally gastric mucosal damage is prevented by a balance between the damaging agents and the mucosal defences.

Damaging agents
ACID (+ pepsin)

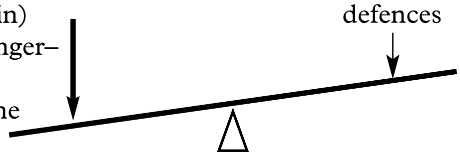
Mucosal defences
Surface mucus layer
+ bicarbonate
Epithelial cell integrity

Balanced

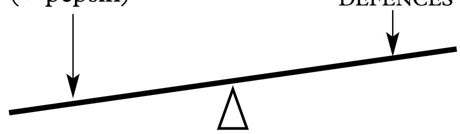


Peptic ulceration results from imbalance.

(a) INCREASED ACID (+ pepsin) e.g. Zollinger–Ellison syndrome — Normal defences



(b) Normal ACID (+ pepsin) — DECREASED DEFENCES



Although the mechanisms in gastric and duodenal ulcers differ, in both *HELICOBACTER PYLORI* infection is important.

Gastric ulcer

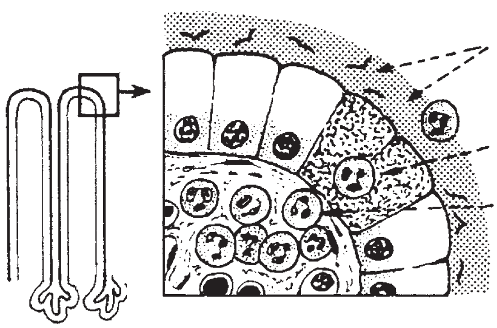
Colonisation of antrum by *H. pylori* (70%).

NSAIDS → REDUCED MUCOSAL DEFENCES

DUODENO-GASTRIC REFLUX (including bile; aggravated by smoking) → REDUCED MUCOSAL DEFENCES

ACID (usually low or normal) → REDUCED MUCOSAL DEFENCES

High magnification



Duodenal ulcer (DU)

The main factors are **hyperacidity** and *H. pylori* infection (>90% of cases).

H. pylori → Gastric infection → Increased gastrin → **Hyperacidity** (genetic factors also important) → METAPLASIA → *H. pylori* infection of duodenum

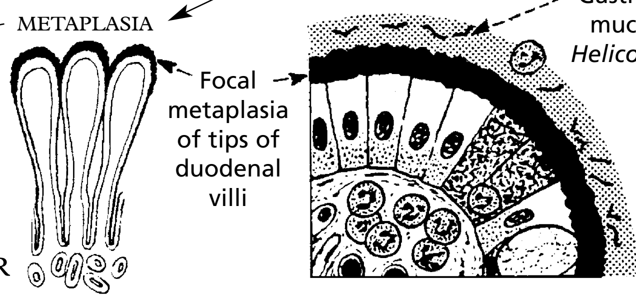
H. pylori → *H. pylori* infection of duodenum

+ other factors, e.g. stress, smoking

ACID

↓

DUODENITIS → ULCER

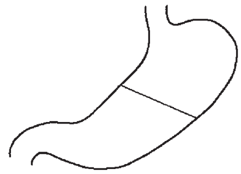


Note: DU is cured when *H. pylori* is eliminated and acid reduced.

GASTRIC CARCINOMA

This important tumour has an especially high incidence in Japan, Chile and Eastern Europe. Its incidence has fallen in the United Kingdom and the USA since the 1930s.

Morphologically, there are several types.

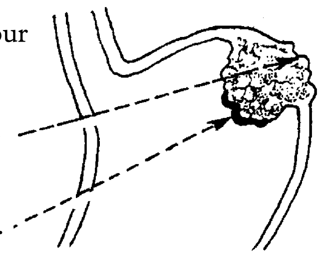


Tumours may occur at the cardia or distal stomach. Different aetiologies apply.

1. **EXOPHYTIC**

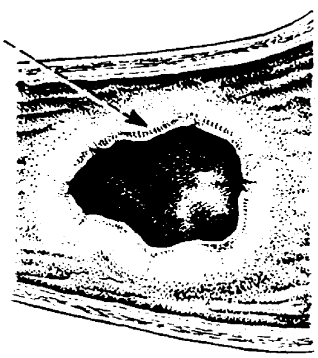
These exophytic tumours are commonly seen in the fundus.

Eventually the tumour spreads through the stomach wall to the serosa and is often ulcerated on the surface.

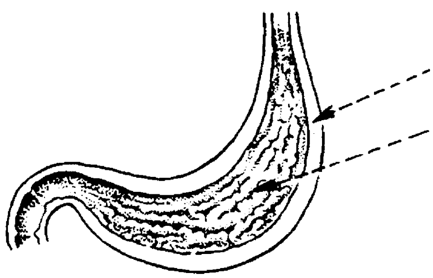


2. **ULCERATIVE**

These tumours, often in the antrum, produce large irregular ulcers with a rolled edge.
The rolled edge rather than the ulcer base should be biopsied.



3. **DIFFUSE PATTERN**

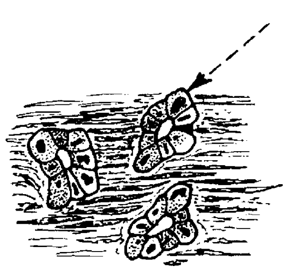


In this form of tumour the entire gastric wall is thickened. Ulceration is usually minimal, but the mucosal folds are prominent.

This is sometimes knows as 'leather-bottle stomach' (linitis plastica).

Histologically, gastric cancers tend to fall into one of two types:

(a) **Intestinal**



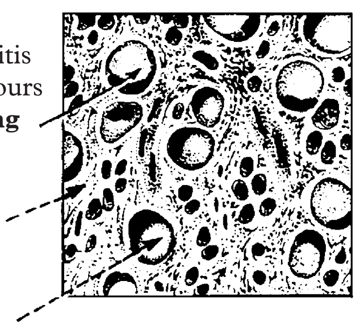
Malignant cells arranged in **acini** invade through the muscle of the stomach wall.

(b) **Diffuse**

Typically seen in linitis plastica. These tumours consist of **signet ring cells.**

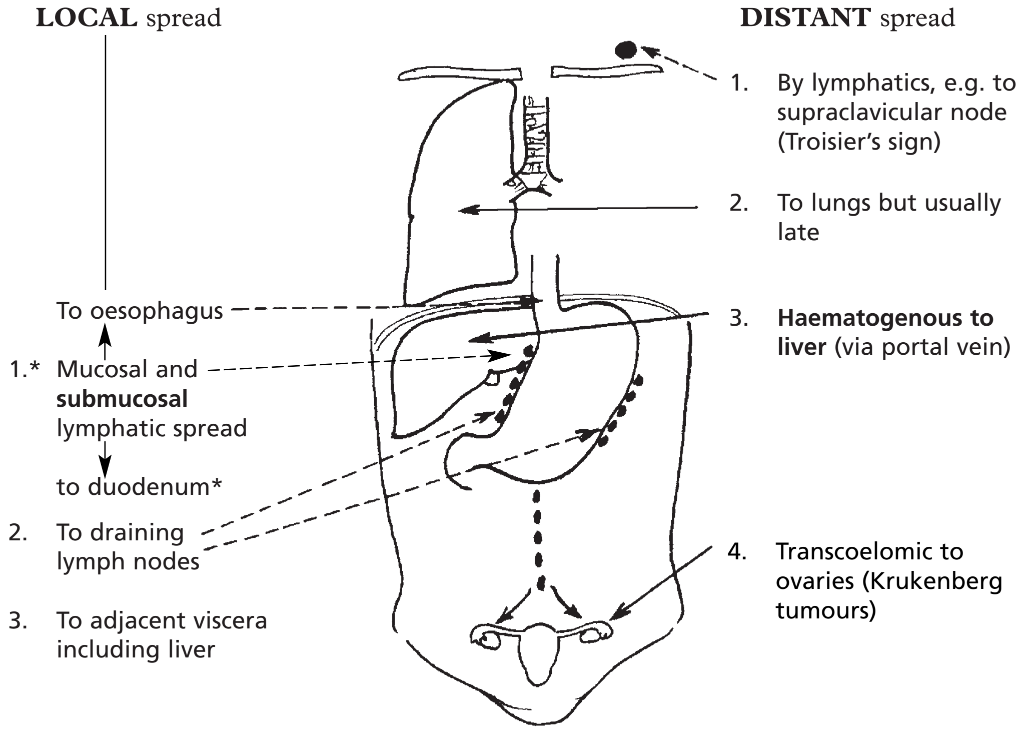
Extracellular mucin may also be present.

Globules of mucin push the nucleus to one side.



GASTRIC CARCINOMA

Gastric carcinomas are aggressive tumours with both local and distant spread.

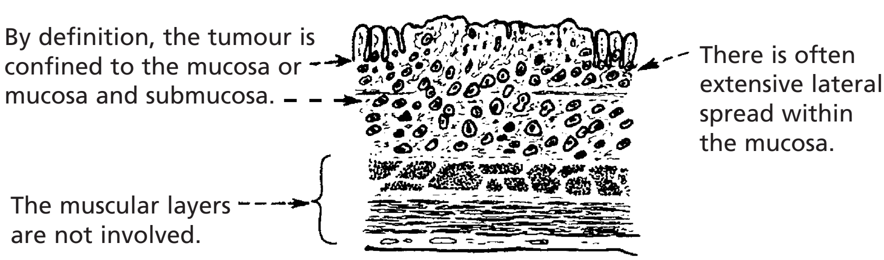


* *Note:* The duodenal mucosa is resistant to direct mucosal spread.

Staging is by the TNM system (Tumour: Nodes: Metastases).

EARLY GASTRIC CANCER

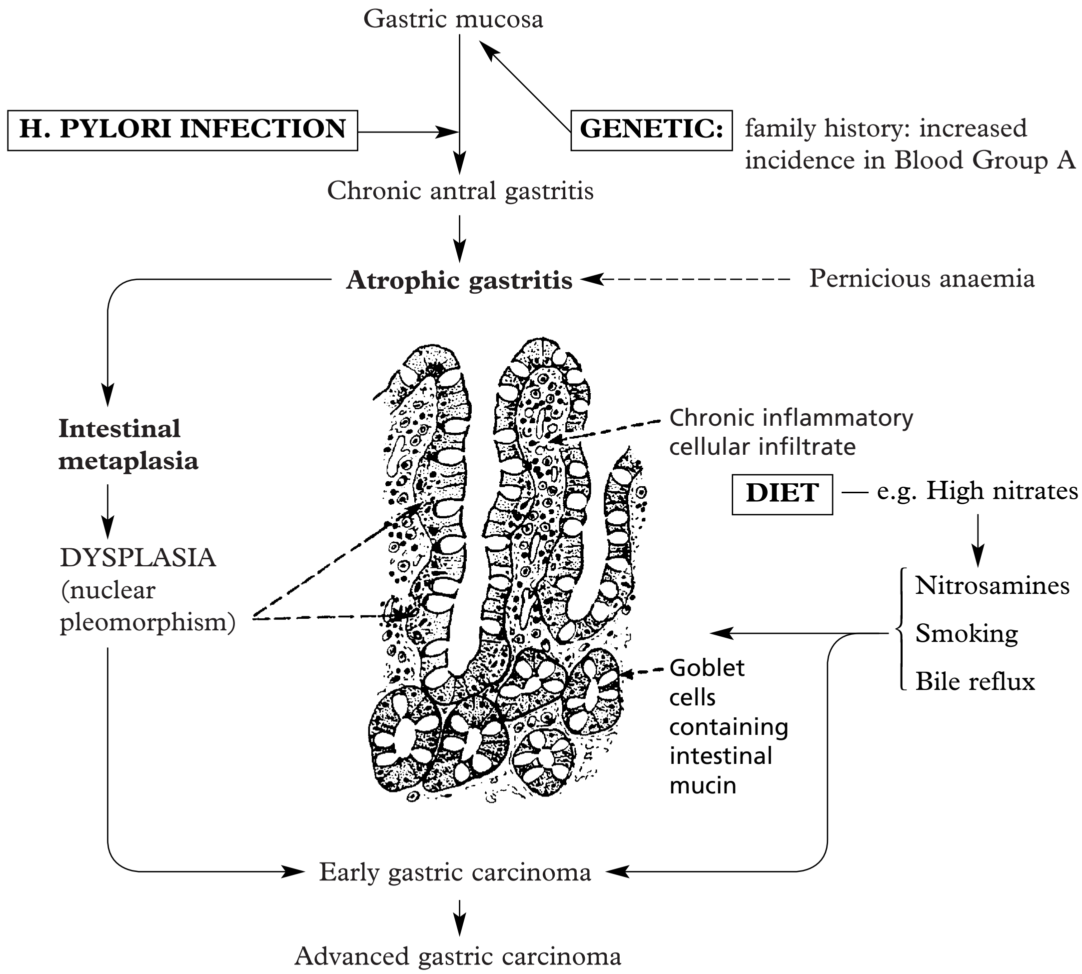
Early gastric cancers are common in populations where there is screening, e.g. Japan. The prognosis is far better than for deeply penetrating 'advanced' tumours.



GASTRIC CARCINOMA

Aetiology
It has long been recognised that gastric cancer occurs in achlorhydric states, especially with chronic atrophic gastritis.

It is now clear that *Helicobacter pylori* is a major carcinogenic factor for these tumours arising in the distal stomach. Acid reflux is responsible for those in the proximal stomach.



OTHER GASTRIC TUMOURS
Benign gastric polyps are often seen at endoscopy. Fundic gland polyps are found in patients on proton pump inhibitors.

Gastrointestinal stromal tumours (GISTs) arise from within the stomach wall and may cause haemorrhage. All are potentially malignant.

GASTRIC LYMPHOMAS account for 5% of gastric malignancy. They are usually 'B' cell lymphomas of MALT type (p.436). They are strongly associated with *Helicobacter pylori* infection and some lymphomas respond to eradication of *H. pylori*.

SMALL INTESTINE – MALABSORPTION

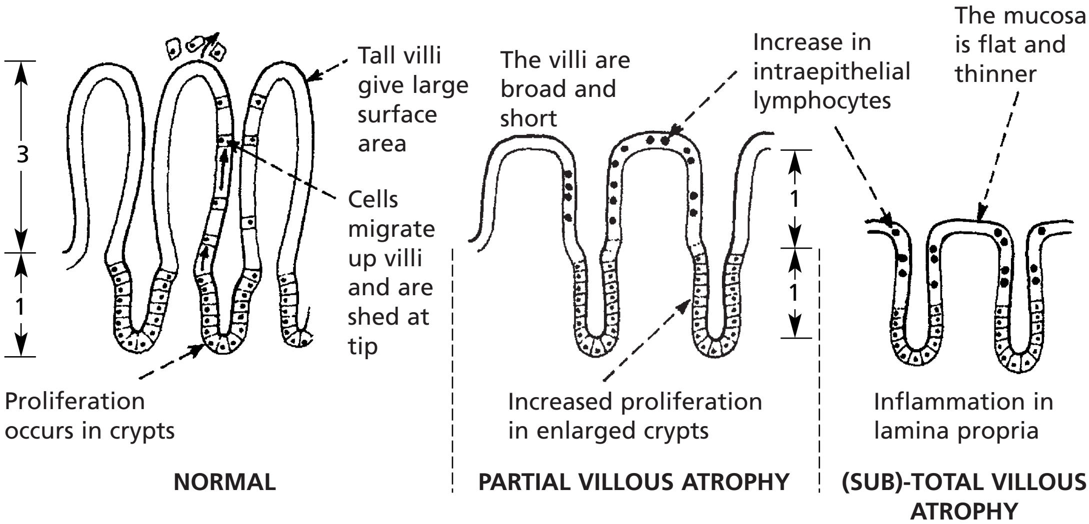
The main function of the small intestine is digestion and absorption of food. **Malabsorption** may be due to disorders of the small bowel, pancreas and biliary tract.

COELIAC DISEASE

This important cause of malabsorption is due to sensitivity to gliadin, a component of the wheat protein **gluten**. The clinical features depend on the age at presentation.

Infancy – Failure to thrive, diarrhoea (steatorrhoea).
Childhood – Growth retardation, nutritional deficiencies, e.g. anaemia.
Adults – Anaemia, altered bowel habit, weight loss.

In coeliac disease there is partial or complete villous atrophy.



These changes are seen in biopsies of small bowel, usually the distal duodenum by endoscope. The changes revert to normal if gluten is removed from the diet. Serological tests are available with anti-endomysial antibodies or directed against tissue transglutaminase (tTG).

The basic mechanism is as follows:

Genetic predisposition (e.g. HLA DQ2 or HLA DQ8 +ve) + Exposure to gliadin → LOSS OF ORAL TOLERANCE TO GLUTEN → Auto-immune attack on SI → ↑Loss of enterocytes → Crypt hyperplasia (regeneration) / VILLOUS ATROPHY → MALABSORPTION

Patients with coeliac disease also have increased prevalence of autoimmune diseases, e.g. diabetes, autoimmune thyroiditis and of lymphocytic colitis, a cause of diarrhoea.
They are at increased risk of developing small bowel **lymphoma**.

MALABSORPTION

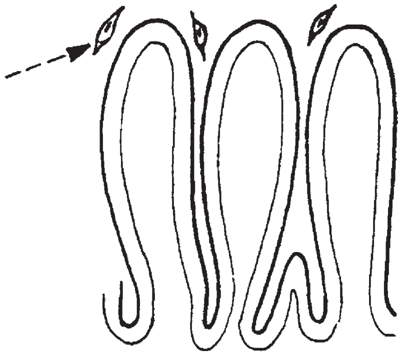
Other causes of malabsorption in the small bowel include:

1. **TROPICAL SPRUE**

This is a disease of unknown aetiology occurring in the tropics. Villous atrophy is seen and patients develop steatorrhoea, weight loss and deficiency of B12 and Folate, leading to megaloblastic anaemia. Treatment with folic acid and antibiotics cause the disease to remit.

2. **GIARDIASIS**

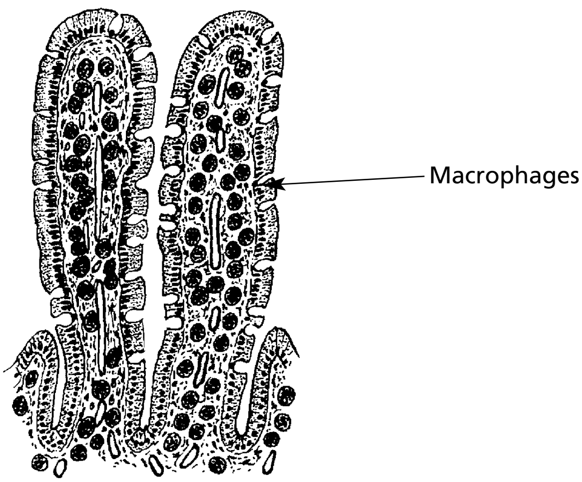
An infection with the protozoan *Giardia lamblia*, giardiasis is associated with diarrhoea and malabsorption. Patients with hypogammaglobulinaemia are especially at risk.



3. **WHIPPLE'S DISEASE**

In this rare condition, mainly of middle aged men, malabsorption, arthritis, lymphadenopathy and skin pigmentation are seen.

Large macrophages fill the lamina propria. They contain mucopolysaccharides (are periodic acid Schiff (PAS) positive). Electron microscopy shows numerous intracellular bacteria – now thought to be a gram-positive organism *Tropheryma whippelii*. Antibiotics are curative.



4. **CROHN's DISEASE** (p.309)

5. After **SMALL BOWEL RESECTION**

6. **BIOCHEMICAL DISORDERS** e.g. disaccharidase deficiency, abetalipoproteinaemia

7. **BACTERIAL COLONISATION** of the small bowel, e.g. Blind Loop Syndrome.

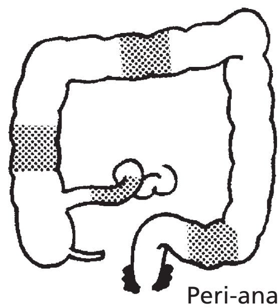
Pancreatic diseases, e.g. cystic fibrosis (p.375) and obstructive jaundice (p.341), also cause malabsorption.

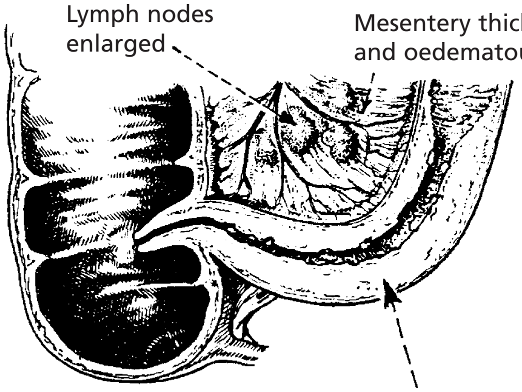
CROHN'S DISEASE

Crohn's disease and ulcerative colitis are two forms of **non-infective inflammatory bowel disease.** They have similarities and striking contrasts (p. 311).

CROHN'S DISEASE

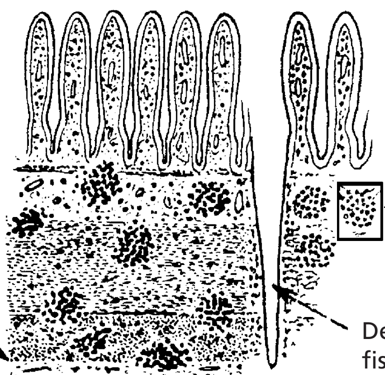
Patients, usually young adults, present with diarrhoea, abdominal pain and weight loss. Although the disease can affect any part of the GI tract from the mouth to the anus, the great majority of lesions are seen in the distal *small bowel* and *colon*.

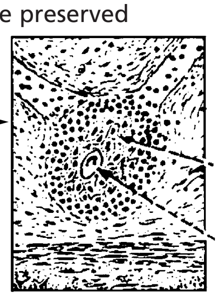






In its classic form, 'regional ileitis', the terminal ileum is thickened and the lumen narrowed and ulcerated.



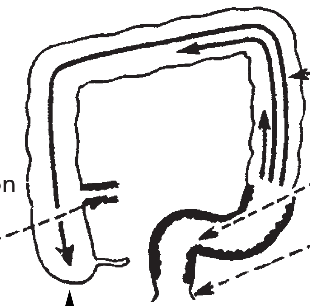


LOCAL COMPLICATIONS

Transmural inflammation ⟶ adhesions between viscera; fistulae to bowel, bladder, vagina.
Lumenal narrowing ⟶ intestinal obstruction.
Ileal involvement ⟶ malabsorption, especially of Vit B12.
Cancer ⟶ increased risk of colonic and **small intestinal** cancer, but not so great as the risk of colonic cancer in ulcerative colitis.

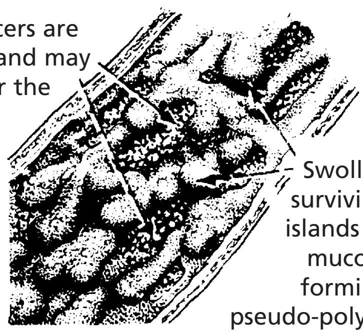
ULCERATIVE COLITIS

Clinical features
Patients, usually young adults, present with diarrhoea, often bloody. The disease has a remitting/relapsing course. In severe cases weight loss and anaemia are common. The disease begins in the rectum and shows continuous spread proximally.



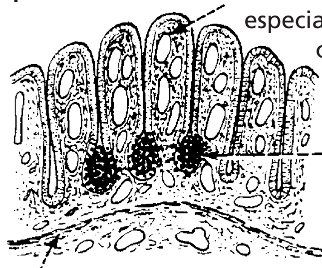
The whole colon is affected in 20% of cases.

In the established disease the **gross appearances** are striking.

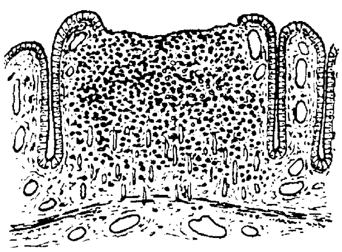


Microscopy shows the evolution.

Early phase

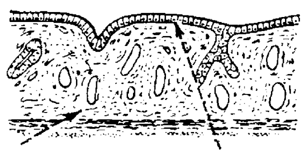


Established phase



The inflammation is usually **confined to the mucosa**

Periods of remission occur when many of the ulcerated areas heal



LOCAL COMPLICATIONS

Toxic megacolon: In a small number of patients inflammation is very severe and the colon becomes greatly dilated and thinned. There is a high risk of perforation with peritonitis.

Dysplasia and Colonic cancer: Patients with (a) early onset, (b) total colonic involvement and (c) long-lasting (10–20 years) disease have a greatly increased risk. These patients require colonoscopic surveillence with biopsy to look for dysplasia and cancer.

CROHN'S DISEASE AND ULCERATIVE COLITIS

The aetiology of these two conditions is uncertain. Both have mild familial tendency (approximately 10%). Infectious causes have been suggested but never proven.

Intestinal epithelial dysfunction may allow entry of bacterial components stimulating mucosal immune responses. Food allergy and stress may be involved in ulcerative colitis. Ex-smokers and non-smokers have a higher risk of ulcerative colitis; the converse is true for Crohn's disease.

EXTRA-GASTROINTESTINAL COMPLICATIONS – both diseases.

1. Eye disorders – conjunctivitis and uveitis in <5%.
2. Joints – seronegative arthritis with spinal and peripheral joint involvement approximately 15% (p.621).
3. Liver – sclerosing cholangitis and cholangiocarcinoma may be seen in ulcerative colitis, but very rarely in Crohn's disease.
4. Erythema nodosum and pyoderma gangrenosum may be found in both.

Macroscopic differences in the pathology of UC and CD:

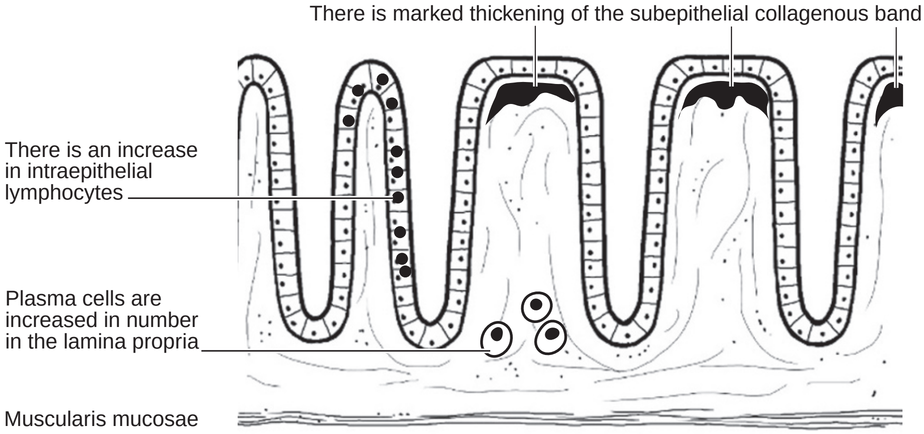
	Ulcerative colitis	**Crohn's disease**
1.	Lesions continuous – mucosal	Skip lesions – transmural
2.	Rectum always involved	Rectum normal in 50%
3.	Terminal ileum involved in <10% (backwash ileitis – mild); caecal patch	Terminal ileum involved in 30%
4.	Granular, ulcerated mucosa; no fissuring	Discretely ulcerated mucosa; cobblestone appearance; fissuring
5.	Often intensely vascular	Vascularity seldom pronounced
6.	Normal serosa	Serositis common
7.	Muscular shortening of colon	Fibrous shortening; strictures common
8.	Fistulae rare	Enterocutaneous or intestinal fistulae in 10%
9.	Malignant change – well recognised	Malignant change – less common
10.	Anal lesions uncommon	Anal lesions in 75%; anal fistulae; ulceration or chronic fissure

It may be impossible to distinguish between ulcerative colitis and Crohn's disease, so called 'indeterminate colitis'.

MICROSCOPIC COLITIS

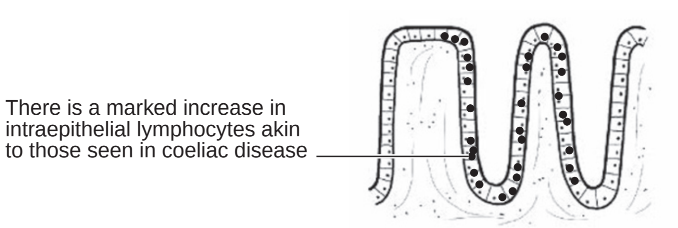
This term describes two forms of colitis which are often overlooked because the colon appears normal on colonoscopy. Both tend to occur in middle aged women who present with chronic watery diarrhoea. The diagnoses depend on identification of characteristic histological findings.

COLLAGENOUS COLITIS



Patients often have co-existing diseases, typically autoimmune, such as rheumatoid arthritis, coeliac disease and diabetes.

LYMPHOCYTIC COLITIS



It is likely that collagenous and lymphocytic colitis are part of the spectrum of the same disease. A relapsing and remitting course is often seen.

INTESTINAL INFECTIONS

Viruses, bacteria, protozoa and worms can all infect the gastrointestinal tract. There are 3 main patterns of infection:

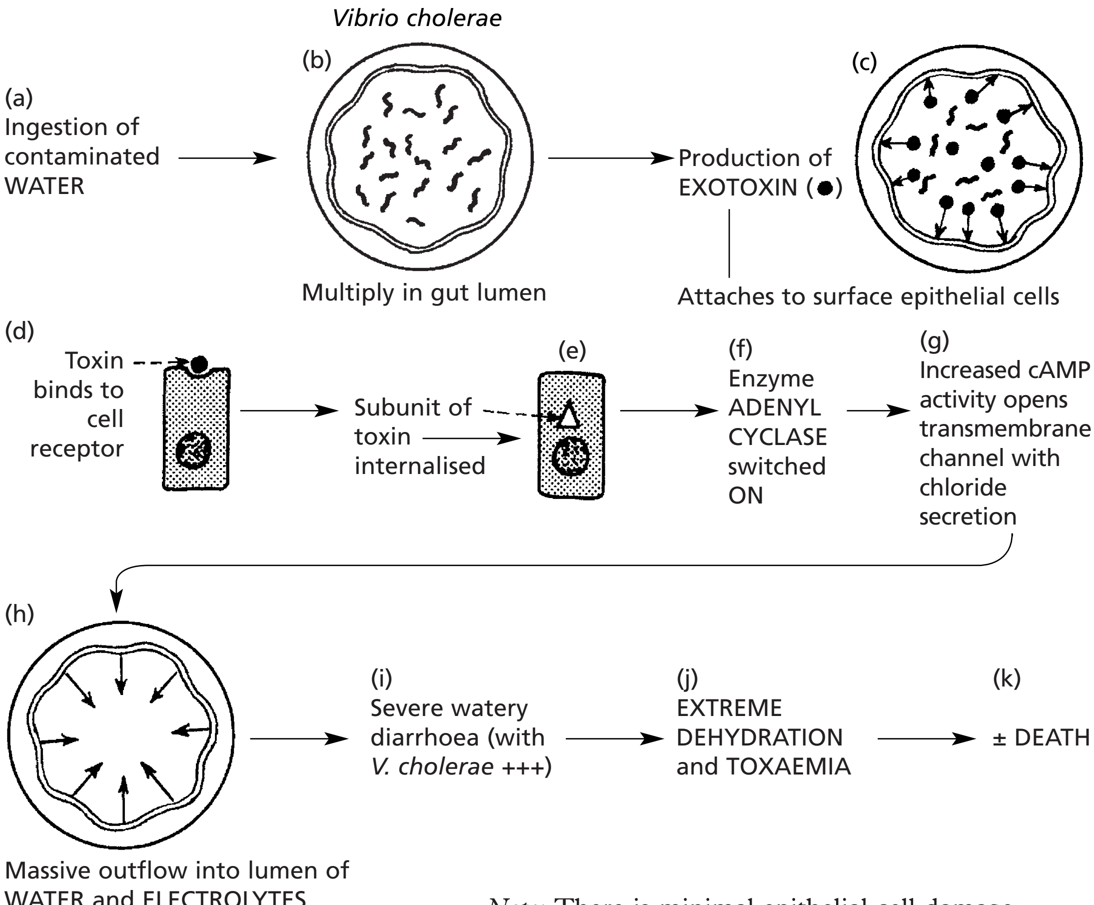
1. Organisms remain within the lumen of the gut and release toxins which damage the surface epithelium, e.g. cholera.
2. Organisms invade the wall of the gut, but remain localised to the gut wall, e.g. bacillary dysentery.
3. Organisms invade the gut wall and spread systemically through the blood stream, e.g. typhoid.

Acute diarrhoeal diseases

In these disorders, infection, mainly of the small bowel, produces little mucosal inflammation, but there is often profuse watery diarrhoea. In adults this may be mild but, especially in infants, dehydration can lead to death.

Responsible organisms include: *E. coli, Vibrio cholerae,* rotaviruses, *Cryptosporidium parvum, Campylobacter jejuni.*

Cholera is the classic example of the effects of toxin production.



Note: There is minimal epithelial cell damage.

INTESTINAL INFECTIONS

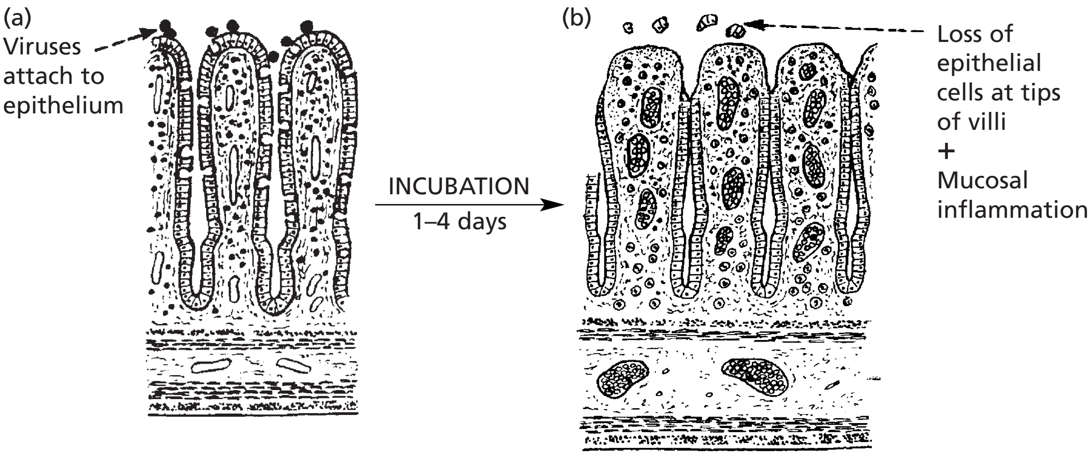
INTESTINAL INFECTIONS *(continued)*

***E. coli* 0157** is a strain which produces exotoxin causing haemorrhagic colitis often complicated by renal failure in the elderly or the haemolytic uraemic syndrome in children. The contamination is on meat or meat products and outbreaks and sporadic cases occur worldwide.

Toxic enteritis (Food poisoning)

Many bacteria release enterotoxins into food before it is consumed: although cooking kills the bacteria the preformed toxin may be heat resistant. *Staphylococcus aureus* and *Bacillus cereus* (in rice particularly) are good examples.

In **ROTAVIRUS infection**, seen especially in children under 5 years, the mechanism is different.



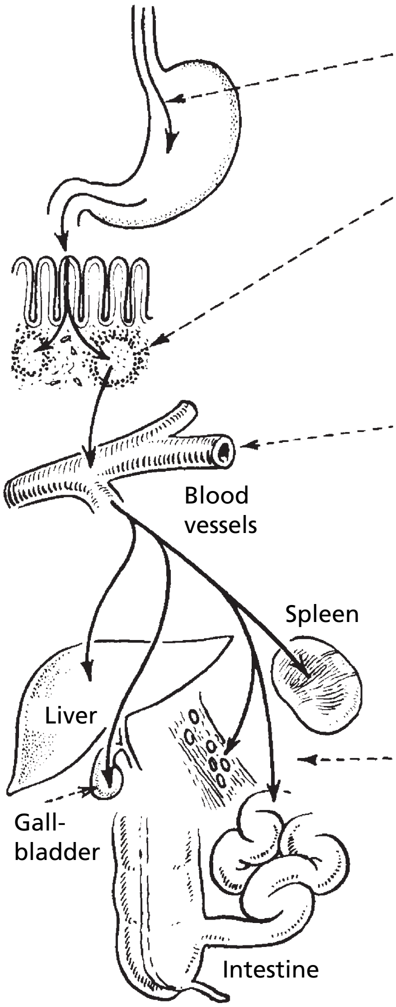
(c) LOSS OF ABSORPTION ⟶ (d) ACCUMULATION of FLUID IN LUMEN ⟶ (e) DIARRHOEA

Note: Recovery is usually rapid and complete, providing dehydration is treated.

TYPHOID

Salmonella infections
Salmonella infections vary from food poisoning, usually a mild inflammation with diarrhoea, to typhoid fever which if untreated is often fatal.

TYPHOID FEVER
Following ingestion of *S. typhi*, the disease process falls into three distinct phases.



Ingestion of *S. typhi* (contaminated water or food)

Phase I
Invasion of intestinal lymphoid tissue and proliferation of bacteria. This phase lasts for 2 weeks.

ASYMPTOMATIC

Phase II
Invasion of blood stream causing bacteraemia.

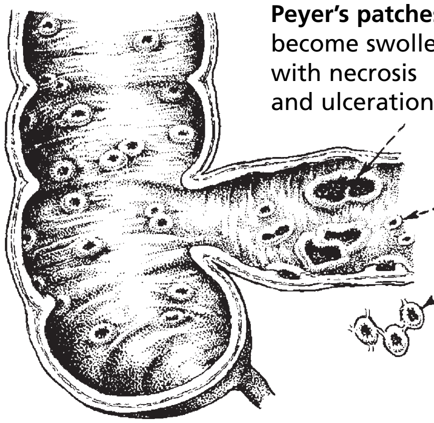
FEVER: TOXAEMIA
'Rose spots' in skin,
Splenomegaly,
Toxic cardiomyopathy,
POSITIVE BLOOD CULTURE,
Appearance of antibodies to *S. typhi* – WIDAL TEST.

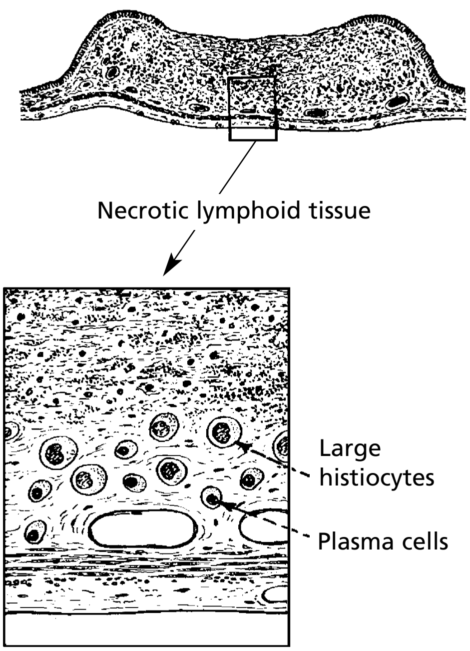
Phase III
Localisation of bacteria in intestinal lymphoid tissue, mesenteric nodes, GALL-BLADDER, liver, and sometimes the bones.

INTESTINAL LESIONS
Endocarditis,
Meningitis,
Arthritis,
FAECAL and URINE CULTURE POSITIVE,
WIDAL TEST – RISING TITRES.

TYPHOID

TYPHOID FEVER *(continued)*





Sequelae

1. Healing is the usual outcome.
2. Deep intestinal ulceration
   - haemorrhage.
   - perforation and peritonitis (usually fatal).
3. Persistent infection (1–3%) – usually GALLBLADDER or urinary tract.

   These carriers appear healthy but are an important source of outbreaks.

PARATYPHOID FEVER

This disease is clinically indistinguishable from typhoid fever but is usually much less severe.

The pathological changes resemble those of typhoid fever but are commonly limited to a small portion of the bowel. Frequently there is an absence of ulceration.

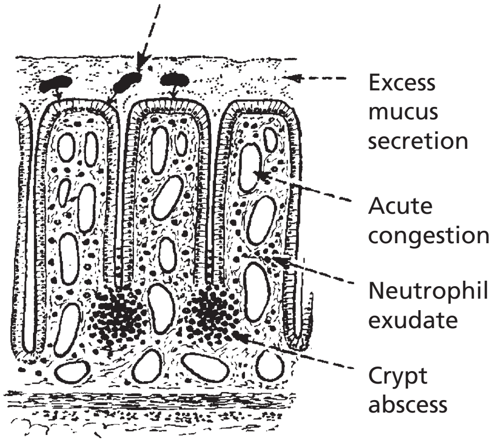
Two serological types of the paratyphoid organism are recognised, A and B. Type B is a common cause of enteric fever in Europe. As in typhoid, patients often become 'carriers'.

Note: TAB vaccination, using antigens derived from *S. typhi* and *paratyphi A and B*, produces a very effective active immunity.

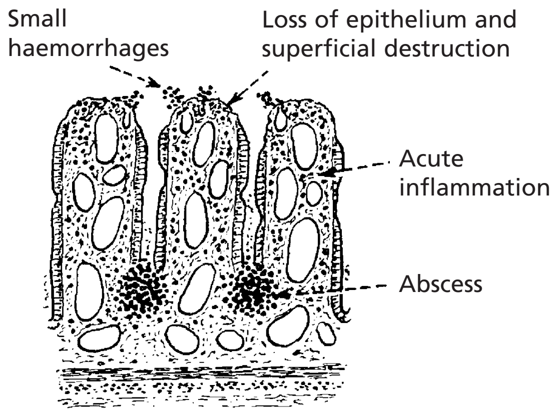
BACILLARY DYSENTERY

This is an acute inflammation of the large intestine, varying in severity according to the infecting agent.

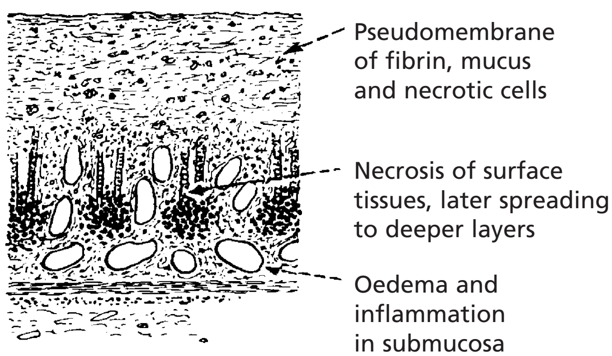
The bacteria adhere to and *invade* the mucosa. They remain localised to the gut.



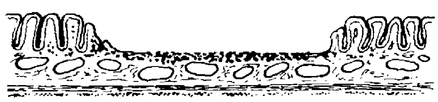
Shigella sonnei
Mild acute inflammation of colon.
Commonest form in the United Kingdom.



Shigella flexneri
Severe acute inflammation.



Shigella dysenteriae
Most severe type, occurs in tropics.



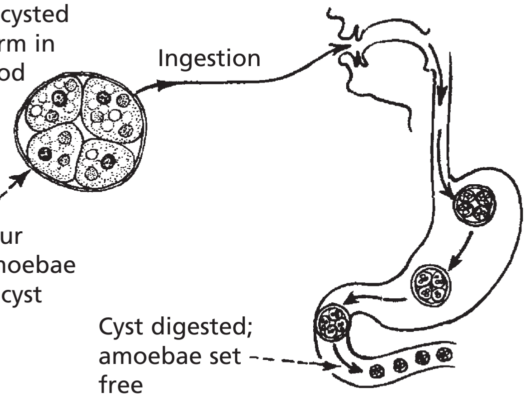
Irregular spreading ulcers with thin shredded margins are formed by shedding of necrotic material.

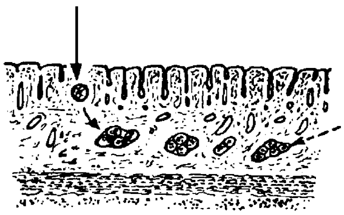
Clinical manifestations
There is acute diarrhoea with abdominal pain, tenesmus and the passage of blood-stained mucus. *S. dysenteriae* infections are often associated with severe toxaemia and sometimes a shock-like condition. Blood, mucus and neutrophils are found in the faeces, and in the early stages the bacilli can be isolated.

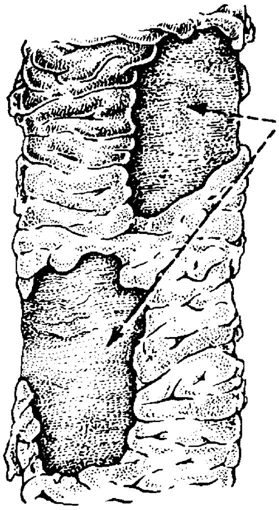
Healing by resolution with complete restoration of the mucosa is usual. Only in exceptional cases does relapse occur with consequent scarring.

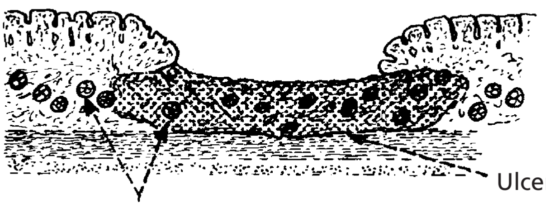
AMOEBIC DYSENTERY

This is due to infection by *Entamoeba histolytica* in food and water. It is most often seen in tropical and subtropical countries.









Healing of the ulcers with fibrosis occurs. The disease persists with overgrowth of fibrous tissue, adhesions to various structures and fistulae may occur. Occasionally the amoebae may invade portal venous tributaries and cause amoebic abscess of the liver (p.360).

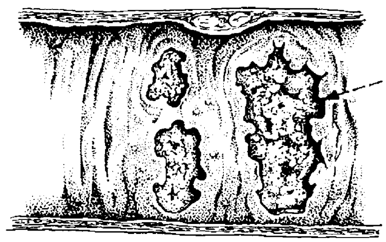
Large numbers of motile amoebae can be found in the faeces during the acute phase of the disease. Later, in the chronic state, they are frequently in an encysted form. Mucus and blood are abundant.

Note: Non-pathogenic amoebae can be found in the colon of healthy individuals.

TUBERCULOUS ENTERITIS AND PSEUDOMEMBRANOUS COLITIS

1. **Primary tuberculous infection** usually follows ingestion of infected milk containing bovine tubercle bacilli and affects the small bowel. It is similar to primary tuberculosis of the lung – a small mucosal lesion and enlarged caseous lymph nodes. These usually heal with fibrosis and calcification.
2. **Secondary tuberculosis**
   This is due to swallowing tubercle bacilli from open pulmonary tuberculosis. The mucosal lesion is prominent and lymph nodes less affected. The lesions start in the Peyer's patches.

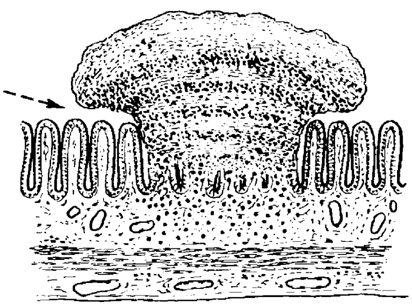


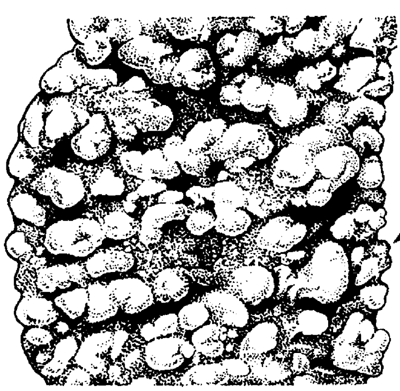


As in the lung, there is a good deal of fibrous granulation tissue surrounding the caseous lesions and the vessels undergo obliteration. For this reason, perforation and haemorrhage are uncommon. Adhesions to other loops of bowel are common and the caseating process may erode through the walls and cause fistula formation with short circuiting and resulting malabsorption. If the fibrous adhesions are dense, obstruction may arise.

PSEUDOMEMBRANOUS COLITIS

Varying lengths of colon show focal inflammation with the formation of surface yellow plaques (pseudomembranes). Most cases are associated with the use in elderly patients of antibiotics.



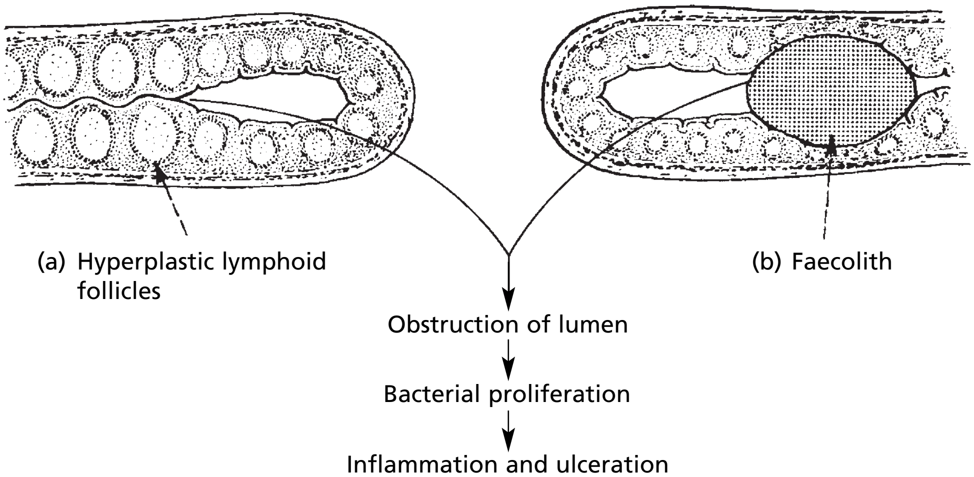


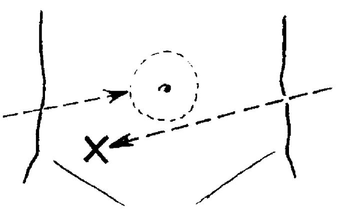
APPENDICITIS

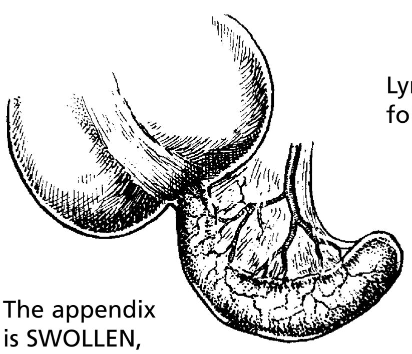
Acute appendicitis is a common cause of abdominal pain requiring surgery, particularly in the West where there is a low roughage diet.

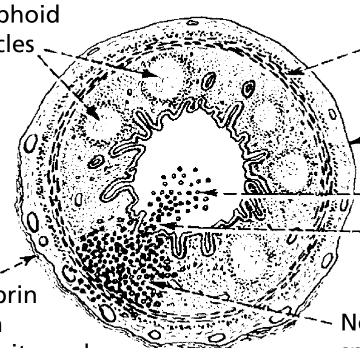
Appendicitis usually follows obstruction of the lumen with distal infection and ulceration. The usual causes are:

(a) Viral infection → reactive hyperplasia of lymphoid follicles. (Infection by *Yersinia enterocolitica* can have similar effects.)
(b) Inspissated faeces (faecoliths).









APPENDICITIS – SEQUELS

If untreated the appendicitis may become suppurative or gangrenous. The following complications are fortunately very rare.

1. **General peritonitis** is the most important complication since it results in toxaemia and may be fatal. It is especially associated with gangrenous appendicitis but may complicate any type of acute appendicitis.

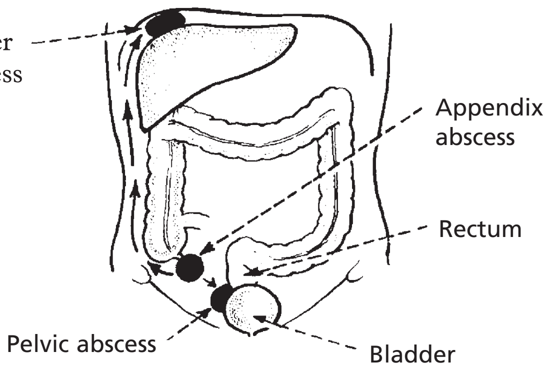
2. **Appendix abscess**
   This arises in the following way:

   Abscess in appendix wall → Perforation + Fibrinous adhesions to adjacent structures (particularly the greater omentum) → Localised abscess in right iliac fossa

Further complications may arise due to spread of infection:

(a) Along the right paracolic gutter to produce a subphrenic abscess between the diaphragm and liver

(b) Into the pelvis to form abscesses around bladder and rectum. In the female the uterus and fallopian tube may be involved.



3. **Adhesions**
   Intestinal obstruction may result from constricting bands, or volvulus may be induced.

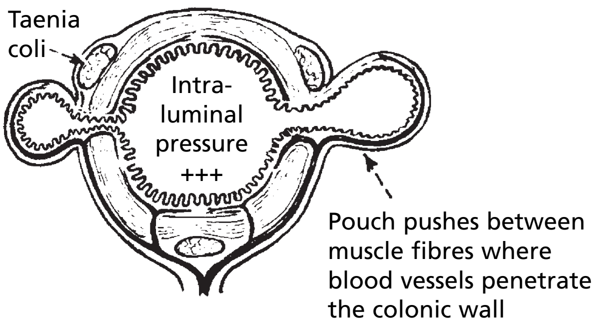
4. **Liver abscesses and portal pylephlebitis**
   These are now rare. They are due to spread of infection to the mesenteric veins resulting in septic embolism. Liver abscesses usually arise from infective emboli, but occasionally there may be a spreading suppurating thrombosis culminating in hepatic sepsis.

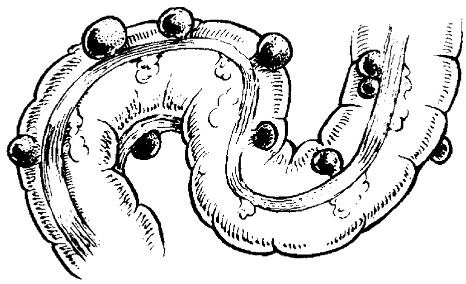
MUCOCELE
This term describes dilatation of the appendix by accumulation of mucus, usually due to a mucinous cystadenoma.

DIVERTICULAR DISEASE

Diverticula are common in the **sigmoid colon**, affecting at least 50% of adults over 60 years in societies where the diet lacks fibre (low residue).

Reduced dietary fibre – low residue in distal colon ⟶ Induces muscular hypertrophy ⟶ Increased intraluminal pressure ⟶ Outpouching of mucosa





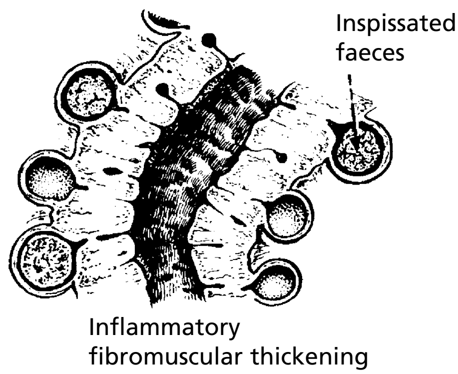
Complications

Diverticulitis is common

Inflammation and ulceration
- abscess formation
- fistulae (e.g.colo-vesical)
- haemorrhage

Repeated attacks
↓
Fibro-muscular thickening
↓
Stenosis

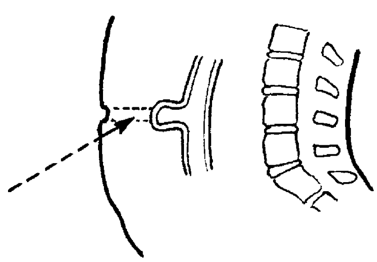
Note: This may simulate carcinoma



Other diverticula are also found in the caecum and small intestine: in the latter, colonisation by bacteria which utilise Vit B12 may lead to macrocytic anaemia.

Meckel's diverticulum of the small intestine is present in 2% of the population.

It is a remnant of the **vitello-intestinal duct** about 60 cm proximal to the ileo-caecal valve.



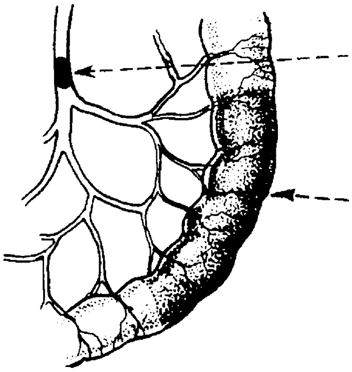
Complications are rare:

(1) The wide communication with the bowel precludes stasis and inflammation.

(2) Rarely ectopic gastric or pancreatic tissue cause local damage (p.301).

ISCHAEMIA AND THE INTESTINES

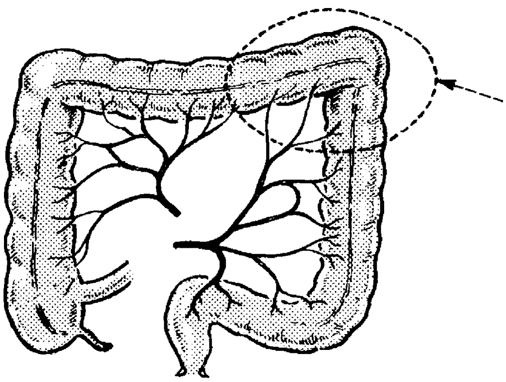
ACUTE VASCULAR OCCLUSION



Occlusion of the superior mesenteric artery is usually due to thrombosis complicating atheroma, or embolism from the left side of the heart or aorta.

Infarction of a loop or much of the small bowel leads to abdominal pain. The infarcted bowel must be removed surgically. Many of these patients are elderly and die.

ISCHAEMIC COLITIS



The colon is more vulnerable to chronic ischaemia than the small bowel.

Ischaemic colitis commonly affects the splenic flexure – the watershed zone. It often occurs in patients with arterial disease with hypotension e.g. due to shock or cardiac failure.

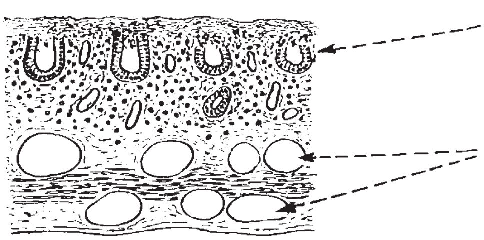
Milder ischaemia ⟶ mucosal ulceration
↓
healing with stricture

Severe ischaemia ⟶ gangrene of bowel

Intestinal ischaemia may also be due to arteritis (p.227), as a side effect of radiation therapy. Drug induced ulcers, e.g. potassium tablets and non-steroidal anti-inflammatory drugs, appear to be due to local ischaemia.

NEONATAL NECROTISING ENTEROCOLITIS

This lesion occurs in premature babies in their first week.



Necrosis and inflammation occur in bowel wall.

Gas bubbles in the submucosa and muscle give a characteristic X-ray appearance.

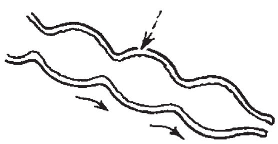
Bowel ischaemia appears to be the initial event, but there is then bacterial superinfection, especially by gas forming organisms.

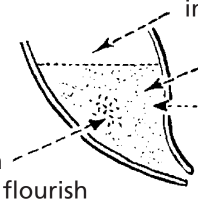
INTESTINAL OBSTRUCTION

Intestinal obstruction can be caused by:
(a) External compression – e.g. hernias, volvulus.
(b) Lesions of the bowel wall – e.g. tumours, inflammatory strictures, intussusception.
(c) Intraluminal blockage – e.g. gallstone ileus (p.367).

The patient may present with colicky abdominal pain, vomiting and failure to pass flatus or faeces.

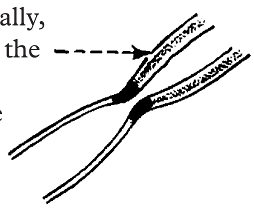
Acute obstruction





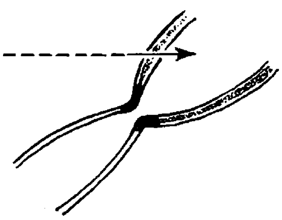
Subacute obstruction

As the condition develops gradually, hypertrophy of the muscle is seen proximal to the obstruction.



Later, obstruction increases and muscle hypertrophy cannot compensate.

Dilatation of the bowel follows with accumulation of gas and fluid.



This gross distension has several effects:

Distension of bowel →
- Retroperistalsis → Fluid passes to stomach → Faecal vomiting →
  - Potassium loss → Weakness of muscles
  - Dehydration
  - Vomit is alkaline → Acidosis
- Pressure impairs blood supply → Viability of bowel impaired → Diffusion of toxic material into peritoneal cavity → Toxaemia
  - (Viability of bowel impaired → Inflammation of bowel wall)
- Bacterial proliferation → Inflammation of bowel wall → Ulceration ('stercoral') → Possible perforation and peritonitis

HERNIA

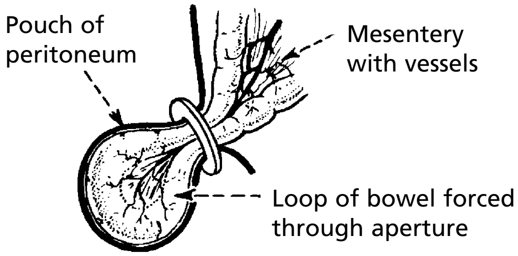
HERNIA

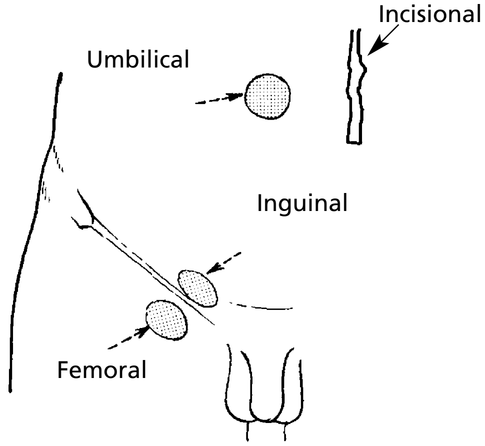
This means the protrusion of peritoneum through an aperture.

When the hernial swelling appears on the surface of the body, it is termed 'external'; those which do not present on the body surface are 'internal'.

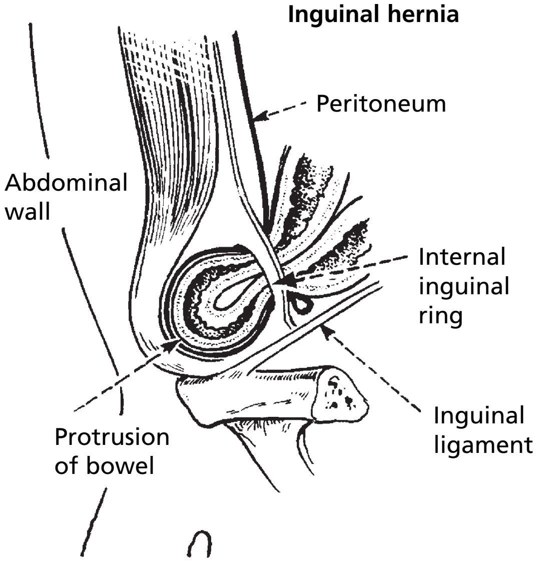
The main complication is protrusion of bowel through the aperture at:

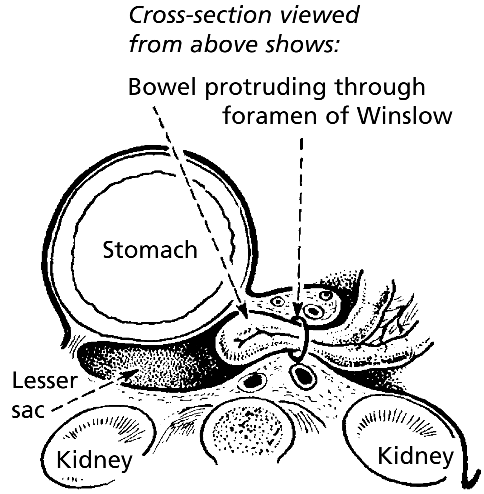
1. Sites of potential weakness in the abdominal wall, e.g. inguinal canal, femoral canal, umbilicus, diaphragm. There may be congenital weakness in some individuals at these sites. In these cases a pouch of peritoneum protrudes through the aperture.
2. Normal peritoneal extensions, e.g. the foramen of Winslow leading to the lesser sac, jejunoduodenal fossa.
3. The abdominal wall following operation due to stretching of scar tissue.





Inguinal hernia





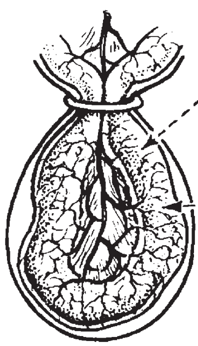
HERNIA – COMPLICATIONS

Complications of hernia
Initially, when the herniated portion of bowel is small it can be pushed back into the abdominal cavity – *reducible*.

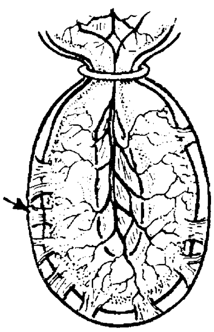
Increased intra-abdominal pressure, e.g. during muscular exertion, coughing or straining due to constipation, helps to induce the herniation, tends to make it progressive, and secondary changes occur.

Raised abdominal pressure
↓
Increase in size of hernia
↓
Hernia impossible to return to abdomen – *irreducible*

↓
Increasing obstruction of bowel
↓
Distension of bowel
↓
Hernial orifice becomes too tight for bulk passing through
↓
Increasing venous obstruction 'strangulation'
↓
Congestion and oedema
↓
Increasing bulk (→ back to hernial orifice becomes too tight)
↓
Complete interruption of circulation
↓
Strangulation and gangrene of bowel



↓
Partial venous obstruction
↓
Exudation into sac
↓
Adhesions between bowel and sac

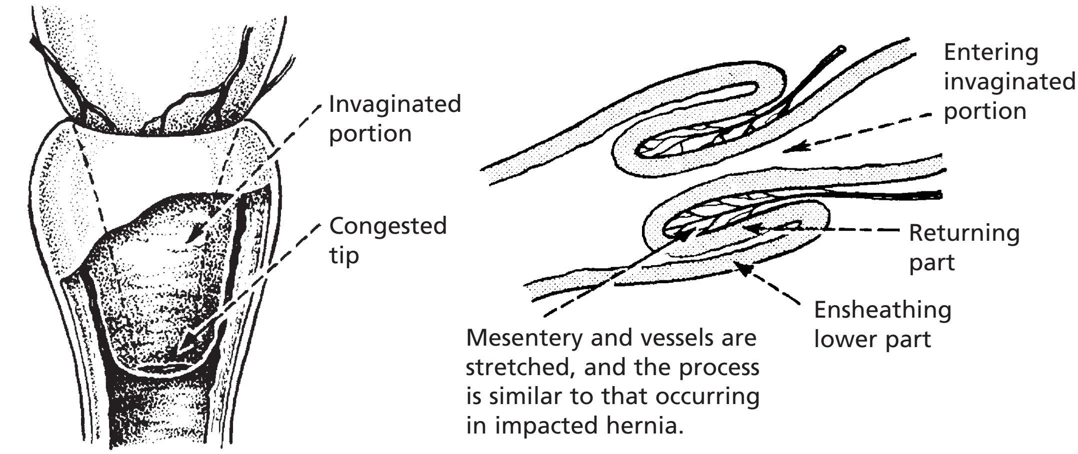


Hernia permanently irreducible – *impacted*



INTUSSUSCEPTION

INTUSSUSCEPTION
This is a condition in which the bowel is invaginated into itself.



Venous return impeded ←
↓
Congestion and oedema of invaginated portion of bowel (→ back to Venous return impeded)
↓
Haemorrhage into lumen of lower portion of bowel | Eventually infarction and gangrene may occur

Sites
The commonest form is the ileocaecal type, the ileum being invaginated into the large intestine with the ileocaecal valve forming the apex. Less commonly, a portion of ileum may pass through the ileocaecal valve. Other sites are occasionally affected, e.g. small intestine or parts of colon.

Clinical manifestations
The patient presents with the signs and symptoms of acute obstruction, a mass in the abdomen and blood is passed per rectum.

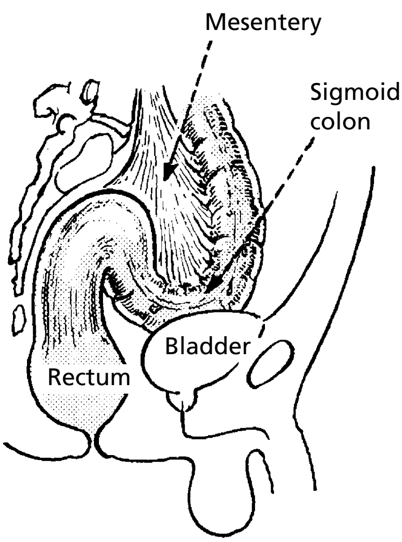
Aetiology
It is thought that most cases arise as a result of a swelling in the intestinal wall which is pushed distally by peristalsis, dragging the wall of the bowel with it. Most cases arise in childhood due to swelling of lymphoid tissue produced by virus infection.

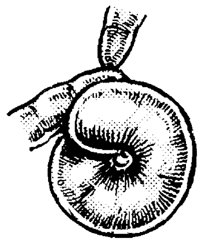
Polypoidal tumours of the intestine may cause intussusception in adults.

VOLVULUS AND HIRSCHSPRUNG'S DISEASE

VOLVULUS

As the name suggests, this is a rotation or revolving of the bowel. It affects bowel with a long mesentery. Another factor is the closeness of the ends of the affected loop.



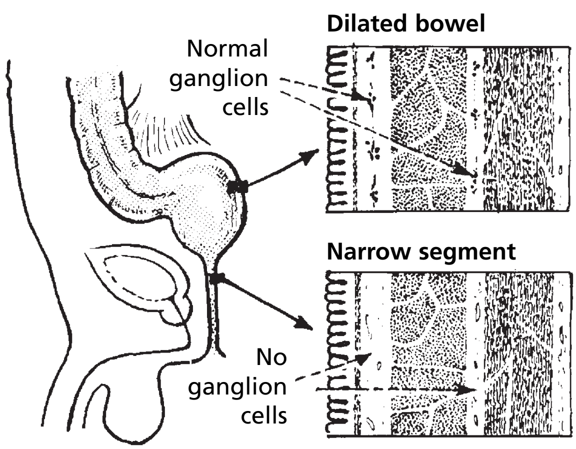


The sigmoid colon is the common site of volvulus. Less commonly, the small intestine is affected.

The subsequent changes are the same as in intussusception.

Twisting of the loop around its own axis
↓ Acute obstruction
↓ Venous return interrupted
↓ Congestion and oedema (→ back to Venous return interrupted)
↓ Infarction and gangrene with peritonitis and shock

HIRSCHSPRUNG'S DISEASE



Hirschsprung's disease is a rare cause of chronic intestinal obstruction. It is due to a congenital absence of ganglion cells in the parasympathetic Auerbach and Meissner complexes of the rectum. Mutations in genes including the RET gene are often responsible.

The aganglionic rectal segment and anus cannot relax and the bowel above becomes grossly distended and hypertrophied.

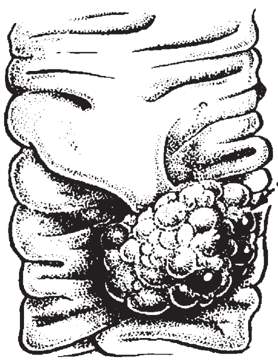
TUMOURS OF THE COLON

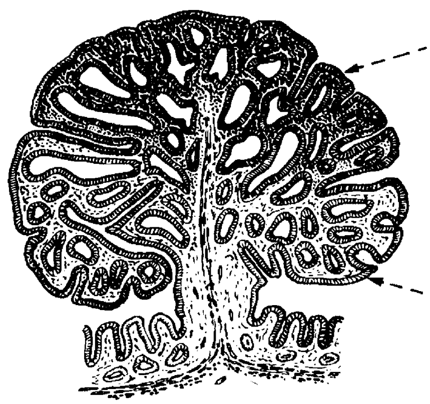
The main tumours of the colon are epithelial – adenomas and carcinomas.

Adenomas – These are important because they may lead on to carcinoma and for this reason bowel screening has been introduced to the UK to detect polyps and early cancers. (Adenoma–carcinoma sequence, p.143)

TUBULAR ADENOMA

The majority of tubular adenomas occur in the rectum and sigmoid colon. In the beginning it is a sessile swelling but soon becomes pedunculated.

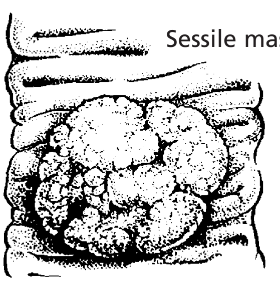


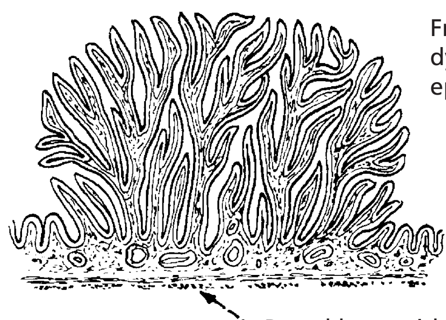


They are common in the older age groups and are frequently multiple.

VILLOUS ADENOMA

Villous adenomas are most commonly found in the rectum. They form a sessile mass which may be quite large and have a delicate frond-like structure.





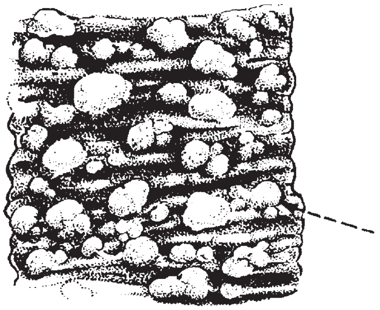
These often present with rectal bleeding.

Very rarely, there is an excessive production of mucus and fluid which may lead to marked loss of potassium, causing muscular weakness.

Many polyps are of mixed variety – tubulo-villous. In pedunculated polyps, the stalk is invaded before the intestinal wall itself.

TUMOURS OF THE COLON

ADENOMATOSIS COLI



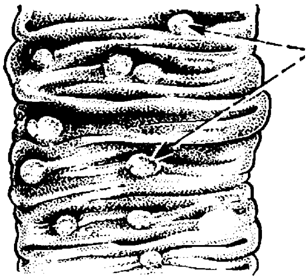
This is an inherited condition (autosomal dominant: 50% of children affected) due to mutation of the APC gene, a tumour suppressor gene on chromosome 5.

Adenomatous polyps are found throughout the entire colon, appearing in late childhood. Carcinoma almost always occurs by the 3rd or 4th decade if colectomy is not carried out.

Polyps may also be seen in the stomach and small bowel.

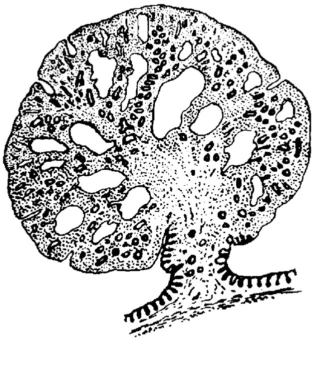
Other Colonic Polyps

1. **HYPERPLASTIC POLYPS**



These are usually multiple and present as a small sessile nodule showing unusual feathery hyperplastic change in the epithelium. They are found in later life and do not become malignant. Some polyps, known as serrated adenomas, have a similar sawtoothed outline but have dysplastic glands and carry the same risk of malignant change as adenomas.

2. **JUVENILE POLYPS**
   These are globular protrusions of the rectal mucosa in children who present with rectal bleeding. They are usually ulcerated and inflamed but probably represent a developmental abnormality. They are occasionally multiple, when there is a small risk of malignancy.



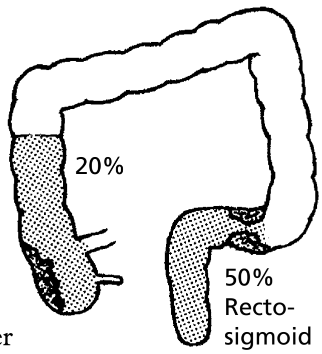
3. **Inflammatory polyps** associated with chronic inflammatory bowel disease are described on page 310.

CARCINOMA OF THE COLON

This malignancy is the third commonest cancer world wide. Tumours in the right and left side tend to present differently.

RIGHT COLON

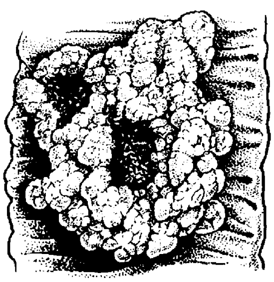
Lumen wide
+
Liquid faeces
↓
NO OBSTRUCTION
Tumours present late
↙ ↙ ↘
Blood loss → Anaemia
Abdominal mass
Liver metastases



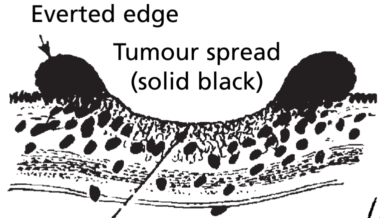
LEFT COLON

Lumen narrow
+
Solid faeces
+
Stenosing tumour
↓
ALTERED BOWEL HABIT
or
OBSTRUCTION
or
RECTAL BLEEDING

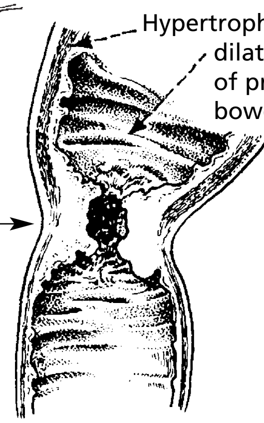
Types of growth

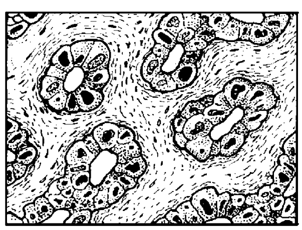


Polypoid carcinoma – mainly in right side, e.g. caecum



Stenosing carcinoma – mainly in left side, e.g. recto-sigmoid





Most tumours are adenocarcinomas

Aetiology

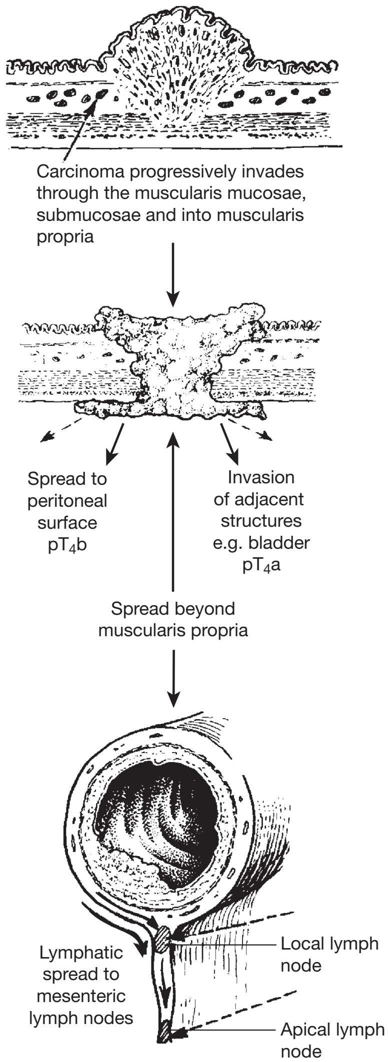
There are genetic and environmental factors.

(a) **Environmental:** Diets rich in animal fat and protein, especially low residue diets.
(b) **Genetic:** e.g. adenomatosis coli (APC gene); hereditary non-polyposis colorectal cancer syndrome (HNPCC) due to mutation of mismatch repair genes.
MOST CASES ARE SPORADIC.
(c) **Pre-existing lesions:**
i. Adenomatous polyps including familial adenomatosis coli.
ii. Inflammatory bowel disease (especially ulcerative colitis).

CARCINOMA OF THE COLON

SPREAD and STAGING (Dukes' staging)

Both Dukes' staging and the TNM classification are used in routine practice. They correlate very well with prognosis. Both systems take into account extent of local invasion, lymph node involvement and distal metastases.



5yr survival %	TNM	DUKES
93	pT_1 Into submucosa	A
	pT_2 Into muscularis propria	A Confined to the bowel
85	pT_3 Beyond muscularis propria	B
72	pT_4 To serosal surface or adjacent organs	B Completely through the bowel wall
	N_0 No nodal involvement	
70	N_1 Metastasis in 1–3 lymph nodes	C Lymph node involvment (irrespective of depth of invasion)
44	N_2 Metastasis in 4 or more lymph nodes	
	M_0 No distant metastasis	
10	M_1 Distant metastasis	D

Blood borne metastases to the liver usually occur later. Extramural vascular invasion is a poor prognostic factor.

Other tumours

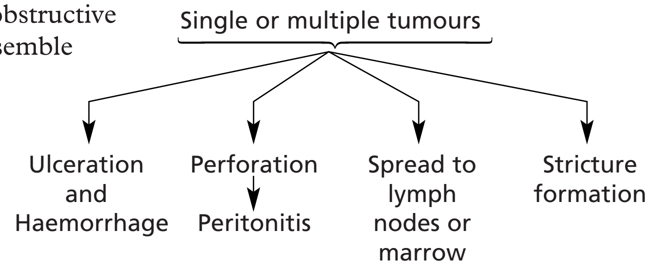
Carcinoid tumour (p.334), lymphoma and connective tissue tumours, e.g. gastrointestinal stromal tumours (GISTs) are occasionally found.

TUMOURS OF SMALL INTESTINE

BENIGN TUMOURS: adenomas, leiomyomas and lipomas are rare, but may cause intussusception (p.327).

Hamartomatous polyps, consisting of glands and muscle, occur in the Peutz–Jeghers syndrome, an autosomal dominant condition. Melanotic pigmentation of the lips and mouth is also seen.

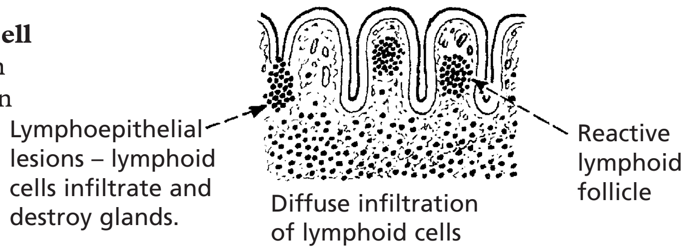
CARCINOMA: adenocarcinoma is 50 times rarer in the small intestine than in the colon. About half occur in the duodenum, mainly around the ampulla of Vater and often arise from adenomas. These present with obstructive jaundice. Tumours in the jejunum resemble those of the colon and may obstruct the lumen. An increased risk of carcinoma is seen in patients with Crohn's disease, coeliac disease and the Peutz–Jeghers syndrome.



LYMPHOMA: these are non-Hodgkin's lymphomas of 'B' or 'T' cell type.

(a) **Enteropathy associated T-cell lymphoma.** These are seen in middle aged patients who often have had coeliac disease for many years.

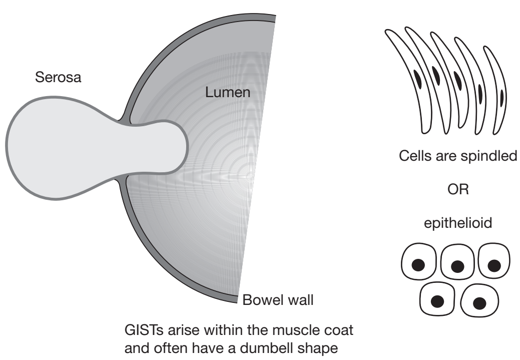
(b) **B-cell lymphomas are usually of MALT type.** These may be of low or high grade.



GASTRO INTESTINAL STROMAL TUMOURS (GISTs)

GISTs occur within the stomach, small bowel and, less commonly, oesophagus and colon. They arise from precursors of the interstitial cells of Cajal (gut pacemaker cells). Mitotic activity and size are the main predictors of malignancy – peritoneal spread and liver metastasis.

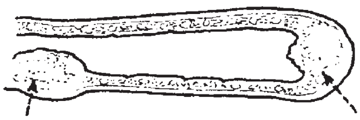
Most are due to activating mutations of the c-kit gene and many respond to modern tyrosine kinase inhibitors.



GISTs arise within the muscle coat and often have a dumbell shape.

CARCINOID TUMOURS

These tumours arise from endocrine cells and can occur in the gut and lung. They are commonest in the appendix and small bowel.

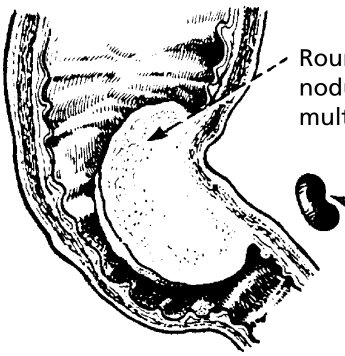


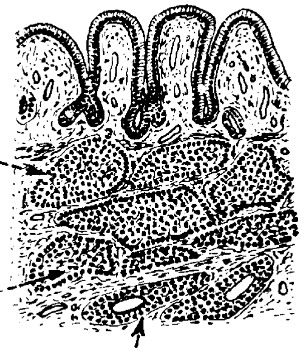
APPENDICEAL CARCINOIDS

These may be incidental findings at appendicectomy or may cause appendicitis.

SMALL BOWEL CARCINOIDS

These are commonest in the ileum.





They contain neurosecretory granules (EM) and express endocrine markers, e.g. chromogranin, synaptophysin. The cells can bind and reduce silver compounds and are known as 'ARGENTAFFIN CELLS'.

CARCINOID SYNDROME

These tumours may secrete a variety of neuroendocrine and paraendocrine substances, in many cases without any apparent clinical functional effects.

However, ileal carcinoids tend to produce peptides: such as 5-hydroxytryptamine (5HT) (serotonin). This is normally destroyed in the liver and lungs: when metastatic deposits are present in the liver the active agents enter the general circulation and produce the CARCINOID SYNDROME, characterised by episodic flushing, diarrhoea and right heart failure.

Excess 5HT

- Hypertrophy of intestinal muscle → fibrosis → 'Obstructive' symptoms diarrhoea
- Vasodilatation → Episodes of flushing
- Fibrin formation → Deposition on valves of right heart → Organisation → Fibrosis → STENOSIS (Pulmonary and tricuspid valves)

THE PERITONEAL CAVITY

PERITONITIS

Acute Peritonitis usually follows inflammation of a viscus,

e.g. 1. Appendicitis, cholecystitis, pancreatitis.
2. Perforation e.g. duodenal ulcer, ruptured diverticulum.
3. Ischaemia – vascular occlusion, volvulus, intussusception.

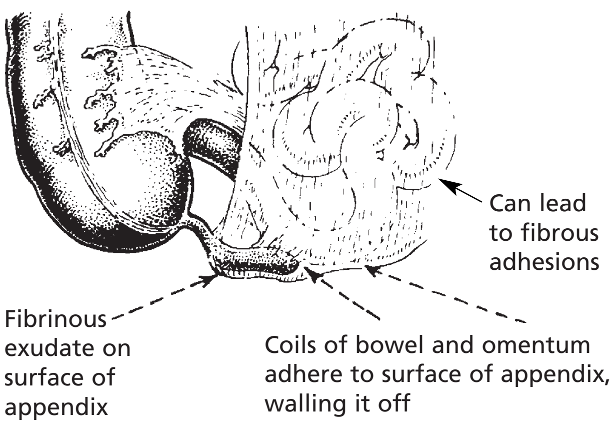
Patients on chronic ambulatory peritoneal dialysis (CAPD) are prone to episodes of peritonitis.

Primary Peritonitis

In the absence of visceral inflammation, primary peritonitis may occur in children with the nephrotic syndrome (pneumococcus) or in adults with cirrhosis (usually coliforms).

Peritonitis can be:

LOCALISED
e.g. appendix abscess



GENERALISED

Bacteria → Endotoxin release → SHOCK

Exudation → Hypovolaemia → SHOCK

SHOCK
(mainly endotoxic)

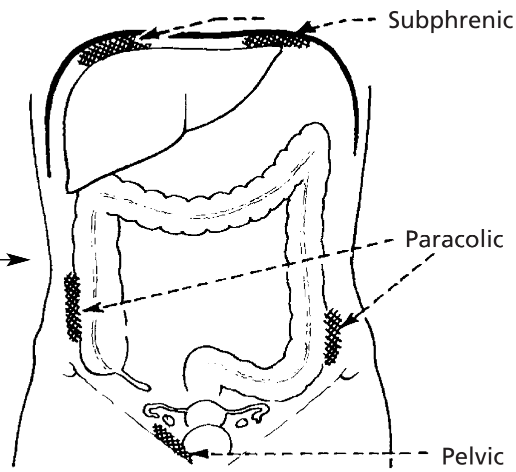
Consequences of peritonitis.

(a) Shock ⟶ death.

(b) Recovery.

(c) Adhesions due to organisation of exudate ⟶ intestinal obstruction.

(d) Localised collections of pus. ⟶



THE PERITONEAL CAVITY

Chronic peritonitis
The most common type of chronic inflammation involving the peritoneum is that resulting from non-resolution of acute peritonitis.

A form of sclerosing peritonitis may complicate long term peritoneal dialysis.

Tuberculosis of the peritoneum is uncommon in Western countries, but frequent in developing countries. It commonly takes one of the following forms:

1. **Serous effusion.** Small grey nodules (tubercles) are usually scattered over the peritoneal surface. In addition, the omentum is more extensively involved with the formation of a large fibrous mass in the upper abdomen.
2. **Caseation.** This can vary in extent, from isolated small masses to diffuse caseation involving most of the cavity.
3. **Adhesive peritonitis.** The cavity may be reduced to small pockets containing serous fluid. The source of infection may be caseous lymph nodes, tuberculous salpingitis or tuberculous ulcer of the intestine.

Ascites
Accumulation of serous fluid can occur:

1. As part of a general oedema from any cause such as cardiac or renal failure.
2. Portal venous obstruction as in hepatic cirrhosis, portal thrombosis or compression of the portal vein by tumour growth.
3. Tumours of the ovary.
4. Tumours of the peritoneum.

Tumours
Secondary tumours are common, due to spread of carcinoma from the stomach, ovary and large intestine.

Eventually loops of bowel are stuck together by tumour and adhesions resulting in 'frozen abdomen'.

Pseudomyxoma peritonei is seen when mucin secreting tumours, e.g. of ovary or appendix spread widely throughout the peritoneum.

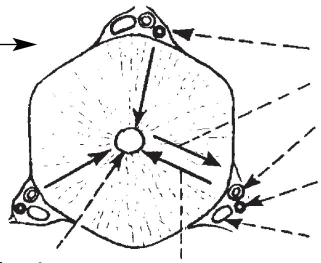
Primary tumours are rare. Mesothelioma is the most important. It is related to the inhalation of asbestos and the pathology is similar to that of mesothelioma of the pleura; large white plaques of solid tumour. Primary carcinomas of the peritoneum are very similar to serous carcinomas of the ovary (p. 511).

CHAPTER 10

LIVER, GALL BLADDER AND PANCREAS

LIVER – ANATOMY

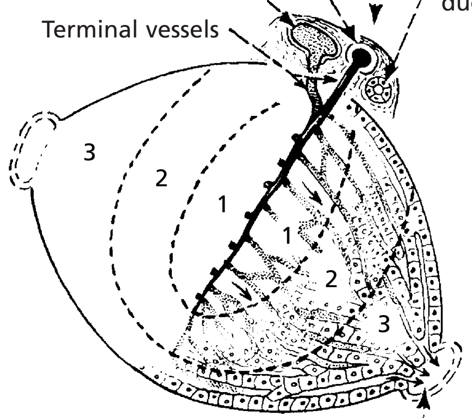
Conventionally the liver was considered to be composed of regular lobules, each arranged around a ‘central vein’ with portal tracts at the periphery.



The acinar concept is now used.

The smallest unit is the simple acinus.

The portal venule and hepatic arteriole both send terminal branches into the acinus (2/3 of the blood supply is portal and 1/3 arterial). They join to form a common trunk which will then contain partially oxygenated blood, and this percolates through the sinusoids to several ‘terminal hepatic venules’ (as in diagram).



In terms of oxygen supply and other nutrients, 3 zones exist.

Zone 1, with the best supply;
Zone 2, with a reasonable supply;
Zone 3, with the poorest supply which makes it most vulnerable to hypoxia.

In Zone 1, glycogen synthesis and glycogenolysis take place. It is also the main area of protein metabolism and formation of plasma proteins. Conjugation of certain drugs takes place.

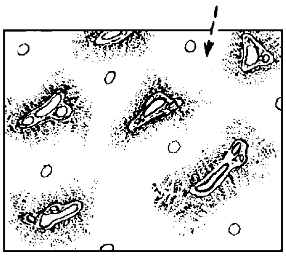
Zone 3 is associated with glycogen storage, lipid and pigment formation and metabolism of certain drugs and chemicals. Zone 2 shares functions with the other zones.

ANATOMY – HEPATIC LESIONS

Adjacent liver acini form a complex architecture best appreciated when diseases affect the varying zones. Factors involved in this include the pO_2 of blood and enzyme function of the zones.

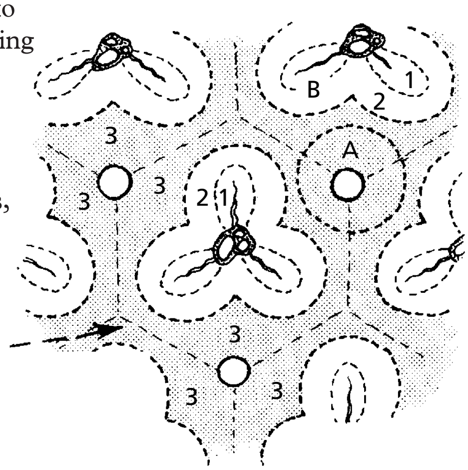
LIVER NECROSIS

Perivenular necrosis

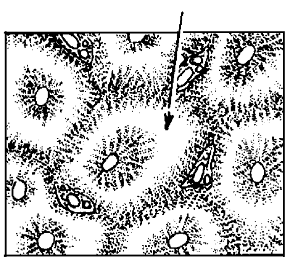


This form is a feature of many apparently unrelated conditions. It is brought about by damage in zone 3 (A in diagram). Thus it is a feature of shock due to circulatory collapse reducing the oxygen supply to zone 3. It also occurs in poisoning with chlorinated hydrocarbons (e.g. chloroform) and drugs, e.g. paracetamol, metabolised in zone 3.

It is important to realise that zone 3, particularly, is continuous from one acinus to another, and in severe cases the hepatic venules are linked together by necrotic tissues.



Mid-zonal necrosis



This is uncommon. It is seen in yellow fever and injury affecting zones 2 and 1 (B in diagram).

Periportal necrosis
Rarely necrosis in zone 1 is due to its metabolism of drugs and chemicals; e.g. phosphorus poisoning causes marked fatty change in the periportal parenchyma, followed by necrosis.

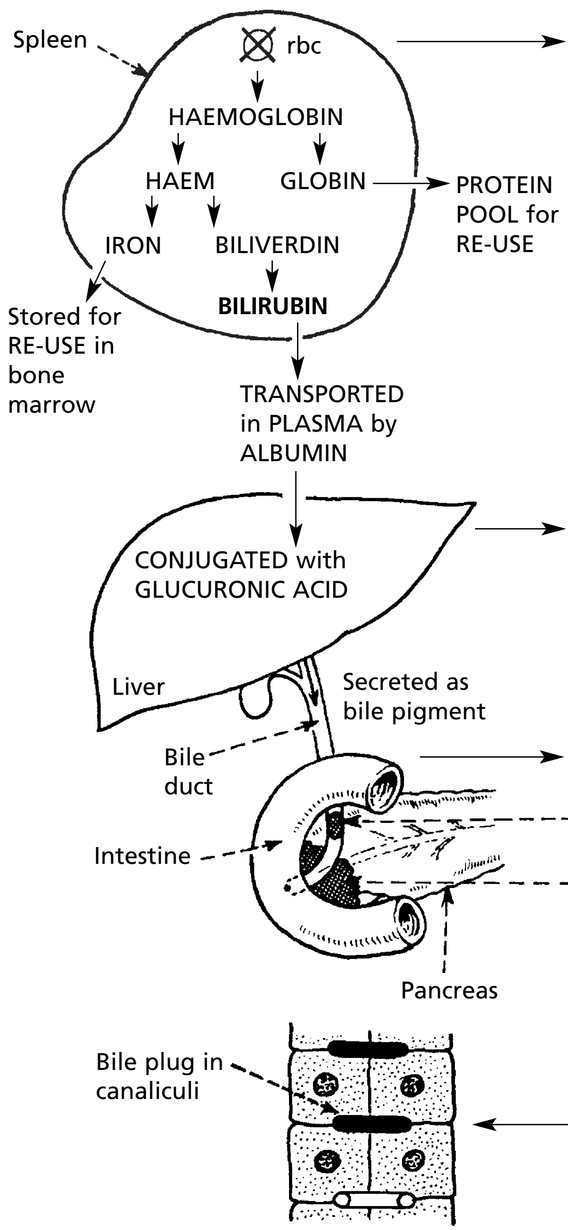
Massive necrosis
This is an unusual lesion which can follow poisoning due to drugs, industrial chemicals or mushrooms. Rarely it is a complication of viral hepatitis.

JAUNDICE

If the serum bilirubin level exceeds 50 μmol/l, the patient becomes jaundiced.

Bilirubin is derived from the breakdown of aged red cells by the macrophage system, mainly in the spleen. It is conjugated to glucuronic acid in the liver and secreted in the bile.

Study of haemoglobin catabolism shows 3 main forms of jaundice:



1. **PRE-HEPATIC JAUNDICE**
due to increased rbc destruction, e.g. haemolytic anaemia.
↑UNCONJUGATED BILIRUBIN (bound to albumin; therefore does not appear in urine – so-called **ACHOLURIC JAUNDICE**).

In NEONATAL HAEMOLYTIC ANAEMIA bilirubin may damage the brain (kernicterus, p.394).

2. **HEPATOCELLULAR JAUNDICE**
e.g. in hepatitis.
Liver cell damage ➝ failure to conjugate bilirubin. In addition, local cholestasis is often also seen.

3. **POST-HEPATIC (OBSTRUCTIVE JAUNDICE)** e.g.
Stone obstructing common bile duct and
Carcinoma of head of pancreas.
FAILURE to EXCRETE CONJUGATED BILIRUBIN
➝ reabsorbed ➝ water soluble
➝ excreted in urine.

FAILURE of BILE to REACH GUT ➝ pale stools.
Intrahepatic cholestasis e.g. steroids and chlorpromazine can lead to cholestatic jaundice.

VIRAL HEPATITIS

ACUTE VIRAL HEPATITIS

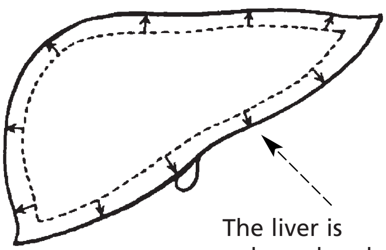
Viral hepatitis is the most important form of hepatitis. It is seen worldwide. Viral hepatitis may be sporadic or epidemic and, depending on the responsible virus, transmitted by the faeco-oral or parenteral route.

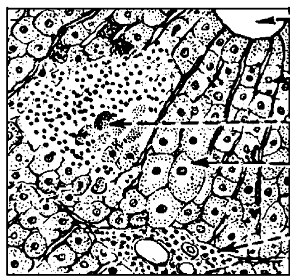
Clinical features

Many episodes of viral hepatitis are subclinical; mild symptomatic cases are characterised by nausea, fever and anorexia. Severe attacks are characterised by jaundice and hepatic failure, and may be fatal.

Pathological features

EARLY stage



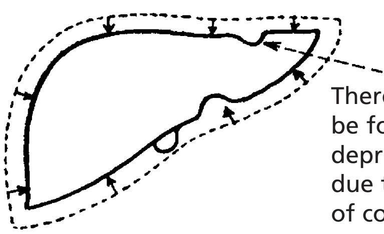


Liver cell necrosis is always present.
It is most marked in Zone 3 (p.338).

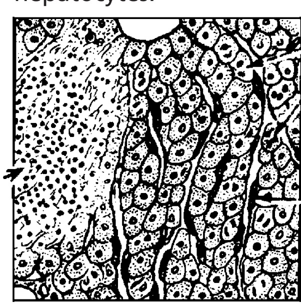
Necrosis may be:

(a) focal (spotty) – scattered as single cells or
(b) more severe – forming areas of bridging between vessels (portal to hepatic venule) or
(c) panacinar – necrosis of complete acini up to massive necrosis of a large part of the liver occasionally occurs. When it does, it is most marked in the left lobe.

LATER stage



There is evidence of healing with mitotic activity in the hepatocytes.



VIRAL HEPATITIS

Biochemical changes

These changes result from liver damage

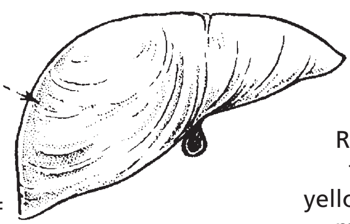
Disruption of bile canaliculi / interference with excretion
↓
Absorption of conjugated bile into blood (levels up to 300 μmol/l.)

Necrosis of hepatocytes
↓
Release of enzymes into blood
↓
Transferase enzymes (ALT, AST) greatly increased

Diminished production of proteins
↓
Coagulation mechanisms upset
↓
Prothrombin times increased

Clinical progress

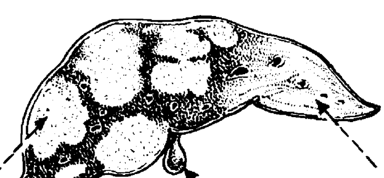
1. In most cases, the disease is self-limiting and complete recovery occurs within 4–6 weeks.
2. Rarely death may occur due to massive (panacinar) liver necrosis.
   (a) In the early pre-icteric stage within 10 days – fulminant hepatic failure.
   (b) In 2–3 weeks. The liver is reduced in size.





This condition was often termed ‘acute yellow atrophy’.

(c) Several weeks later.
At this stage, regeneration is well advanced in places but function is inadequate and progressive failure occurs.



Some types of hepatitis may progress to
3. Chronic hepatitis (p.346),
4. Cirrhosis,
5. Hepatocellular carcinoma.

VIRAL HEPATITIS

At least 5 viruses cause liver damage without significantly damaging other tissues (hepatitis A,B,C,D and E). The features are summarised and then discussed individually.

VIRUS	H**A**V	H**B**V	H**C**V	H**D**V	H**E**V
TYPE	PICO**RNA** VIRUS	HEPA**DNA** VIRUS	RNA FLAVIVIRUS	DEFECTIVE RNA VIRUS	RNA CALICIVIRUS
SPREAD	Faeco-oral	Parenteral	Parenteral	Parenteral	Faeco-oral
INCUBATION PERIOD (weeks)	2–4	4–26	7–8	4–16	4–5
SEVERITY of HEPATITIS	Usually mild	Often severe	Usually mild	Severe	Often mild. Severe in pregnancy
CHRONICITY	No	Approx 5% of adults, 90% of children	Approx 50%	Coinfection 5% Superinfection 95%	No
CARRIER STATE	No	Yes	Yes	Yes	No
VACCINE	Yes	Yes	No	Protected by HBV vaccine if HBV-ve	No

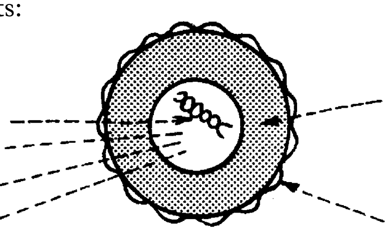
Other viruses which can affect the liver, but also affect other tissues include:

Yellow fever
Herpes viruses – Epstein–Barr, Cytomegalovirus, Herpes simplex
Coxsackie A and B
Lassa fever.

HEPATITIS B INFECTION

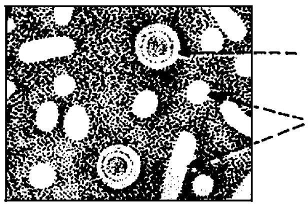
The **hepatitis B virus** is a member of the HEPA DNA virus group. Infection is by the parenteral route – mainly IV drug abuse, blood products and sexual transmission, and in high prevalence areas in childbirth.

The virus has several components:



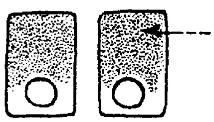
The complete virion is known as the Dane particle. Spherical and tubular structures derived from the surface coat can also be found in the peripheral blood.

These antigens and antibodies to them are the basis for diagnosis of hepatitis B infection.

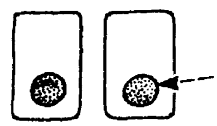


In **histological preparations**

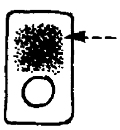
HBsAg accumulates in the cytoplasm of cells – giving a 'ground glass' appearance.

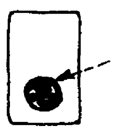


HBcAg is found in the nuclei.

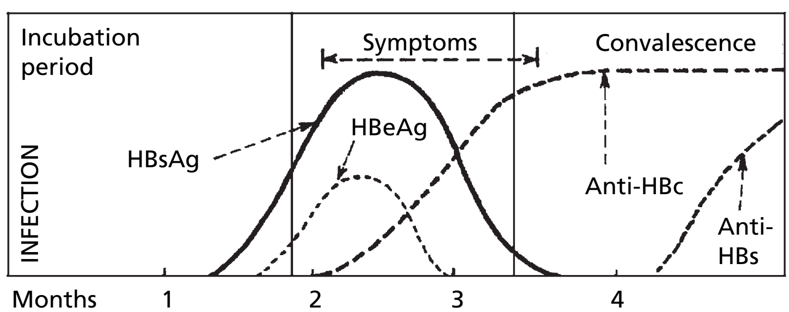


or can be stained by immunocytochemistry.





Serology: Antibodies to the various antigens appear in the blood.

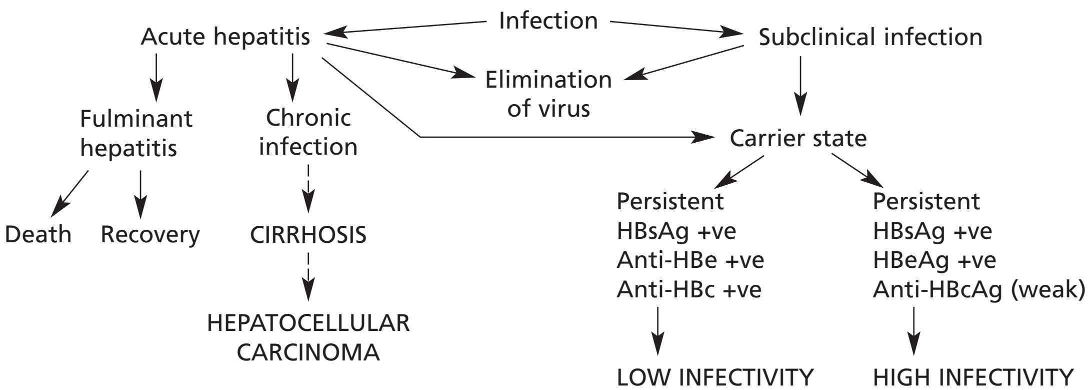


Six weeks after infection the surface antigen (HBsAg) appears in the blood, followed two weeks later by the e antigen (HBeAg), at the time of maximal viral replication.

VIRAL HEPATITIS

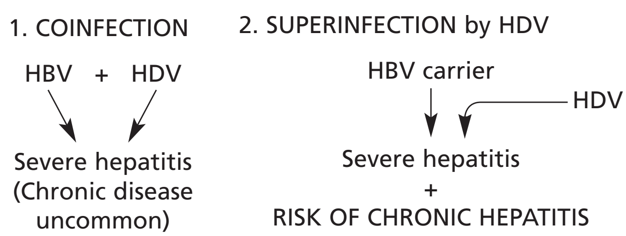
Outcome of Hepatitis B infection

In >90% of cases there is a vigorous immune reaction (cell mediated and humoral) to the virus resulting in its elimination. In the remaining patients, the illness pursues one of several courses:



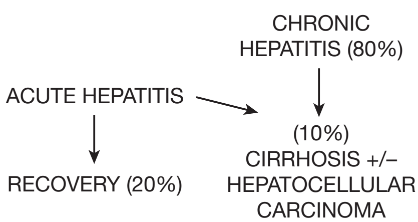
HEPATITIS D

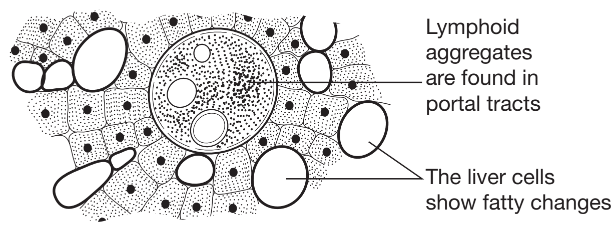
This is a defective RNA virus which requires HB virus for its release and infectivity. There are 2 patterns of infection:



HEPATITIS C

This small RNA virus is transmitted parenterally and is seen in IV drug users or following infected blood transfusion. Acute hepatitis is mild and patients are rarely jaundiced. It is important because of the high risk of chronicity.





HEPATITIS A

This picornavirus is transmitted by the faeco-oral route, especially where hygiene is poor. Hepatitis is usually mild in children, but more severe in adults. IgM antibodies appear in the blood in the acute phase, and IgG during convalescence, thus conferring life long immunity. Chronic liver disease does not occur.

HEPATITIS E

This is most commonly seen in Africa and Asia. Although usually mild, it is particularly severe in pregnant women with a mortality of approximately 20%.

CHRONIC HEPATITIS

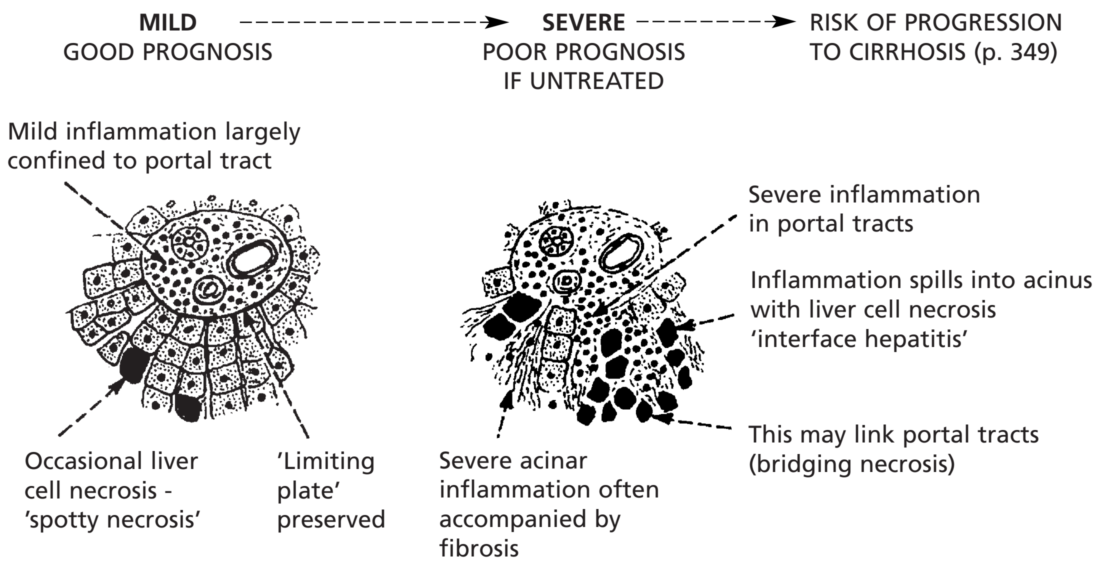
Inflammation of the liver which lasts for more than 6 months is regarded as chronic. (This definition excludes disorders such as alcoholic hepatitis.)

There are 4 main **causes:**

1. **Persistent viral infection** – hepatitis B, D and C.
2. **Autoimmune hepatitis.** This occurs especially in young women. In classic (type I) disease antinuclear and anti-smooth muscle antibodies are present in the serum. Liver specific autoantibodies e.g. to a sialoglycoprotein receptor (ASGP-R) on periportal hepatocyte cell surfaces can also be found. These patients often have other autoimmune diseases e.g. thyroiditis. A smaller subgroup, type II is defined by anti-Liver Kidney Microsomal antibodies (anti-LKM-1) and has a more aggressive disease.
3. **Drugs** – e.g. methyldopa, nitrofurantoin.
4. **In metabolic disorders** – e.g. α_1-antitrypsin deficiency, Wilson's disease (p. 356).

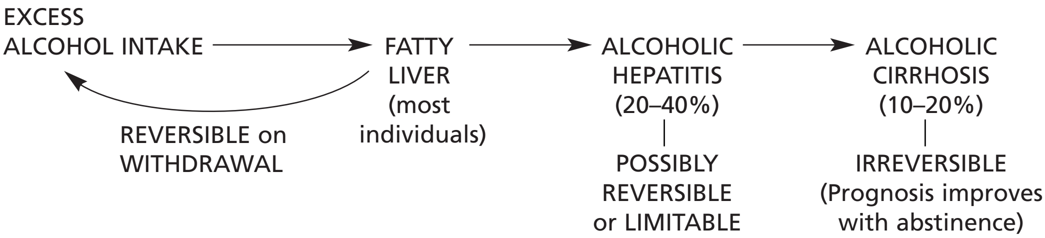
Histologically, three areas of inflammation are seen to varying degrees.

- Portal tract.
- Parenchymal (within the acinus).
- At the interface (limiting plate).



ALCOHOLIC LIVER DISEASE

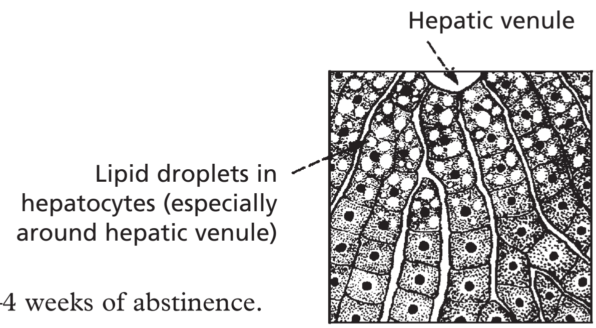
Excess consumption of alcohol is associated with liver disease in three main forms.



The progression from left to right does not occur in all patients: genetic predisposition, coexistant nutritional deficiencies, amount and duration of drinking and other factors determine the risk.

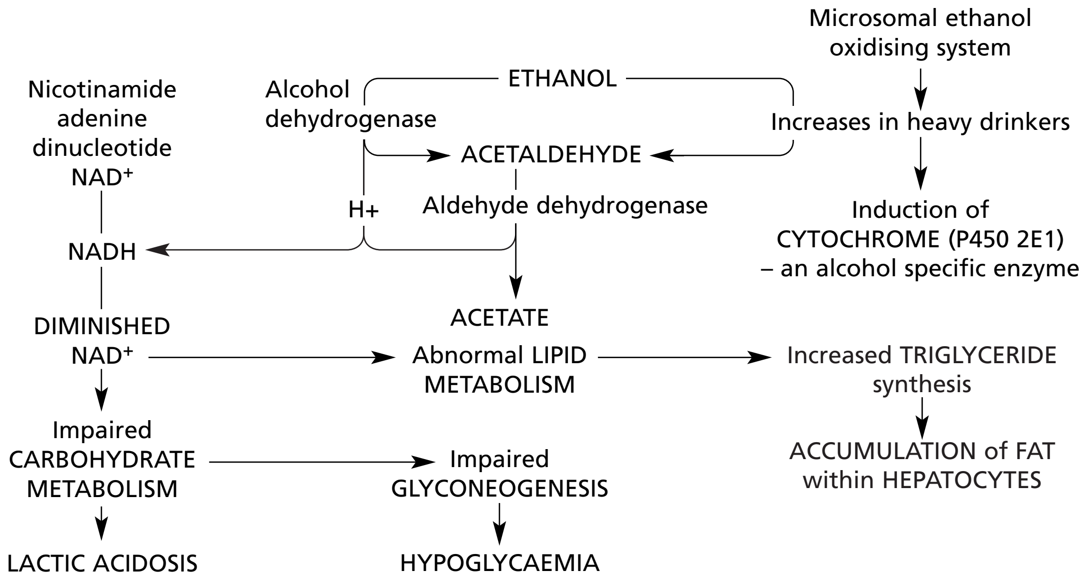
FATTY LIVER

This occurs in most heavy drinkers, even after a single episode of heavy intake. Fat accumulates in the hepatocytes due to abnormalities in the intermediate metabolism of lipids and carbohydrates.



Note: Fatty liver usually resolves within 2–4 weeks of abstinence.

Alcohol metabolism



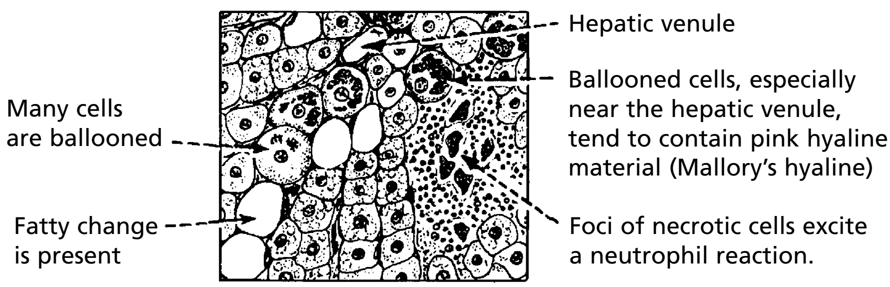
ALCOHOLIC HEPATITIS

In 20–40% of heavy drinkers, alcoholic hepatitis is superimposed on fatty change. This varies from asymptomatic hepatitis to a life threatening condition with nausea, vomiting, abdominal pain and jaundice. Signs of liver failure and portal hypertension may be found.

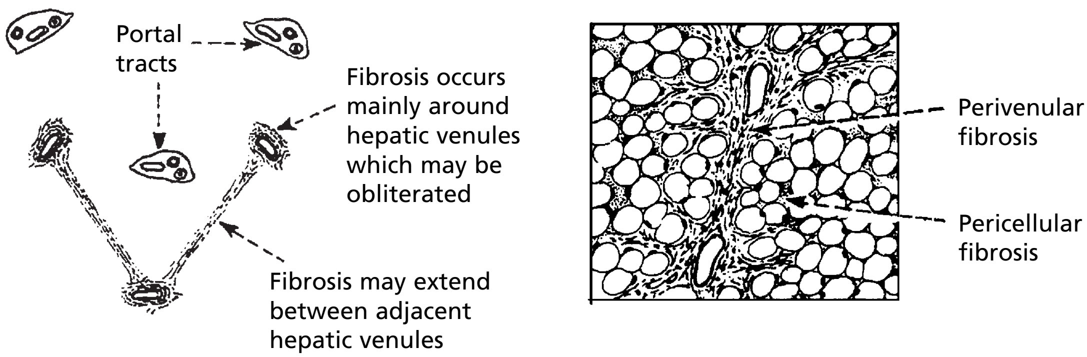
Histologically, the main features are seen around hepatic venules:

1. Liver cell swelling – ballooning.
2. Accumulation of Mallory's hyaline – protein derived from intermediate filaments (mainly cytokeratin).
3. Liver cell necrosis.
4. Neutrophil polymorph reaction.
5. Pericellular fibrosis.

Acute Phase



Progressing to pericellular fibrosis



Alcoholic hepatitis is important as a cause of liver damage, especially because of the high risk of progression to cirrhosis.

The term 'nonalcoholic fatty liver disease' covers a range of fatty disorders of the liver in non-drinkers. This includes simple fatty change and a histologically similar form of hepatitis to alcoholic hepatitis. Diabetes mellitus, severe obesity, jejuno-ileal bypass for obesity and certain drugs (e.g. amiodarone) appear to be responsible.

CIRRHOSIS

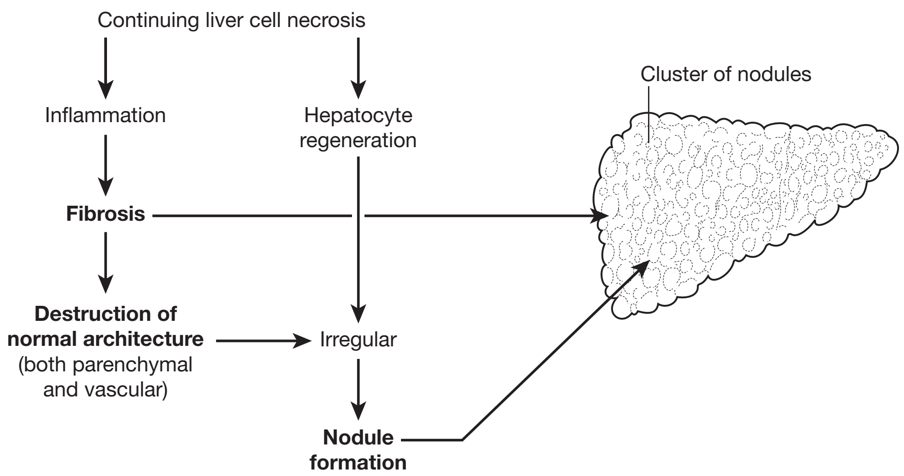
Cirrhosis is the end stage of many liver diseases. It is defined as:

A DIFFUSE process (i.e. the whole liver is affected) characterised by FIBROSIS and conversion of the liver architecture into abnormal NODULES.

Aetiology
There are many causes including:

(i) Drugs and toxins, e.g. alcohol, methotrexate, methyldopa.
(ii) Infections, e.g. Hepatitis B and C.
(iii) Autoimmune diseases – chronic active hepatitis; primary biliary cirrhosis.
(iv) Metabolic conditions, e.g. haemochromatosis, α_1-antitrypsin deficiency, Wilson's disease (excess accumulation of copper).
(v) Biliary obstruction, e.g. gallstones, strictures, sclerosing cholangitis, cystic fibrosis.
(vi) Cryptogenic, i.e. cause unknown.

The **mechanism** common to all cirrhosis is:



Hepatic stellate (fat-storing) cells found in the Space of Disse are activated and transformed into myofibroblast-like cells under the influence of cytokines such as TGFα, PDGF and TGF-β. The activated cells synthesise collagen leading to fibrosis.

The **major complications** of cirrhosis are:

1. Hepatocellular failure.
2. Portal hypertension.
3. Hepatocellular carcinoma.

CIRRHOSIS

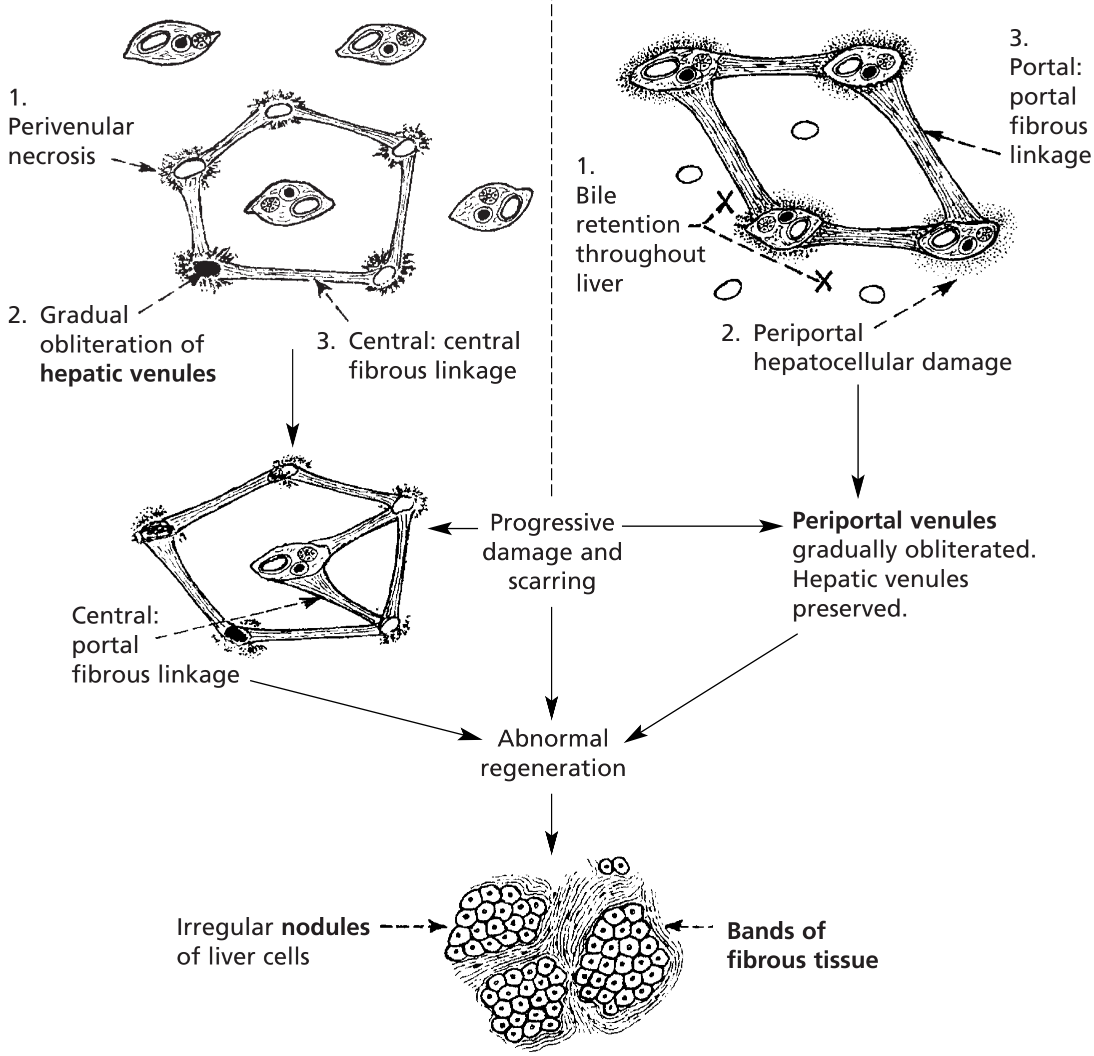
The initiating factor in the progression to cirrhosis is continuing hepatocellular damage. Its location within the acinus (p.338) and also its cause are reflected in the progression to irreversible damage.

The following contrasting diagrams illustrate the differing patterns in cirrhosis depending on the cause.

Alcoholic cirrhosis
develops from alcoholic hepatitis (p.348).

The initial damage is PERIVENULAR (Zone 3).

Secondary biliary cirrhosis
follows long-standing recurrent post-hepatic obstruction: the initial damage is PERIPORTAL (Zone 1).



BILIARY DISEASE

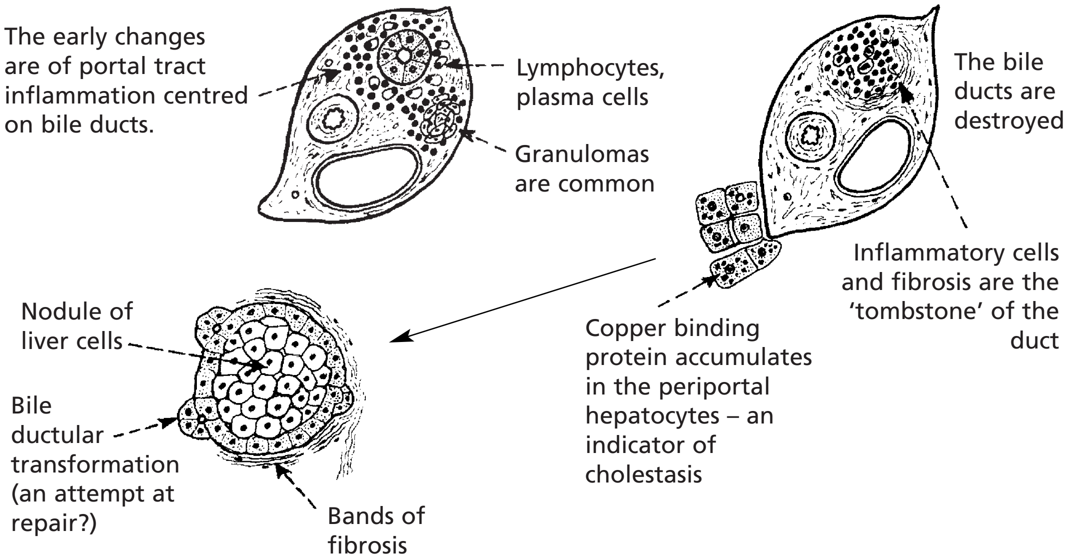
PRIMARY BILIARY CIRRHOSIS (PBC)

This is a chronic disorder mainly affecting middle-aged women. Destruction of intra-hepatic bile ducts leads to scarring and eventually to cirrhosis. Patients typically present with fatigue, itching (from bile salt retention) or jaundice. Hyperlipidaemia is common.

Aetiology

This is an autoimmune disorder. Over 95% of patients have anti-mitochondrial antibodies in their serum. An overlap may be seen with autoimmune chronic hepatitis.

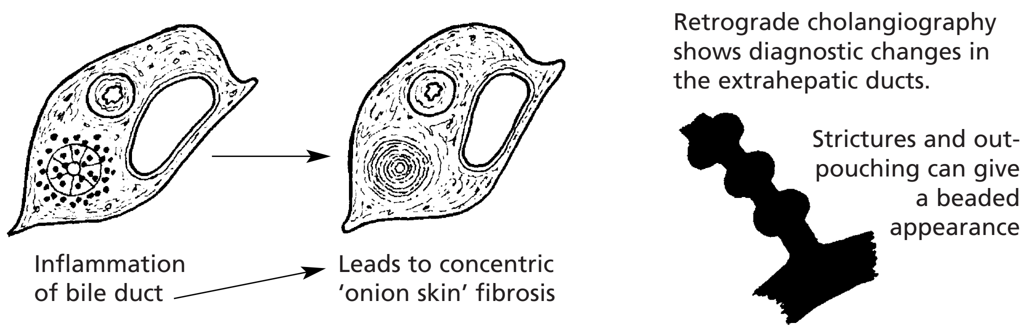
Pathology



Note: Long-standing biliary obstruction can give rise to secondary biliary cirrhosis if untreated.

PRIMARY SCLEROSING CHOLANGITIS

This disease also attacks bile ducts, both intra- and extrahepatic. Men are usually affected and there is a strong association with ulcerative colitis.



The late effects are similar to PBC. Liver failure and bile duct carcinoma are frequent complications.

HEPATOCELLULAR FAILURE

Failure of liver function can be:

1. Acute, with rapid onset (<8 weeks from onset of liver disease), e.g. in cases of massive necrosis due to poisoning, e.g. paracetamol (or, less commonly, acute hepatitis).
2. Chronic and sometimes recurring, of slow onset, e.g. in cirrhosis or chronic hepatitis – representing decompensation.

The mechanism is different in the 2 types.

Acute poisoning
↓
Massive necrosis
↓
Liver mass too small for functional requirements

Cirrhosis
↓ Fibrosis → Increasing vascular obstruction
↓ Hyperplastic liver nodules → Increasing vascular obstruction

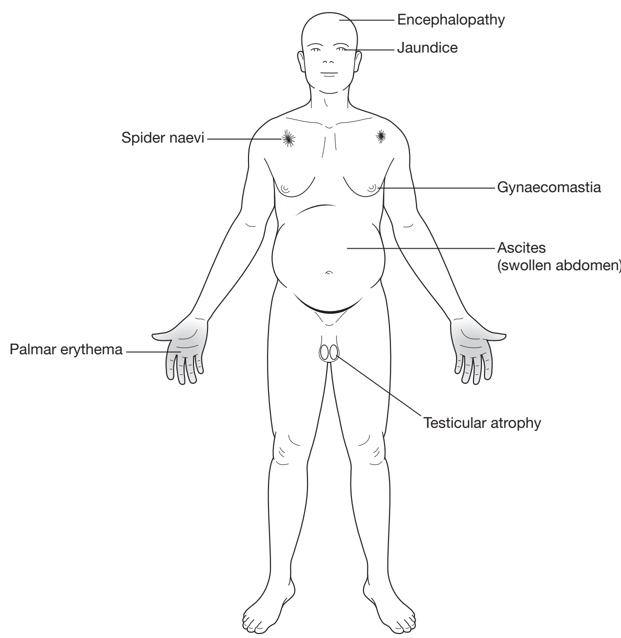
Increasing vascular obstruction
↓ Increasing dilatation of portosystemic anastomoses
↓ Increasing vascular by-pass of liver
↓ Increasing loss of liver function

Increasing vascular obstruction
↓ Increasing isolation of otherwise adequate liver tissue
↓ Increasing loss of liver function

The **cardinal signs of hepatocellular failure are:**

1. Jaundice.
2. Hepatic encephalopathy.
3. Ascites.
4. Bleeding diathesis.

Other features include hypoglycaemia, acidosis and endocrine disturbances.

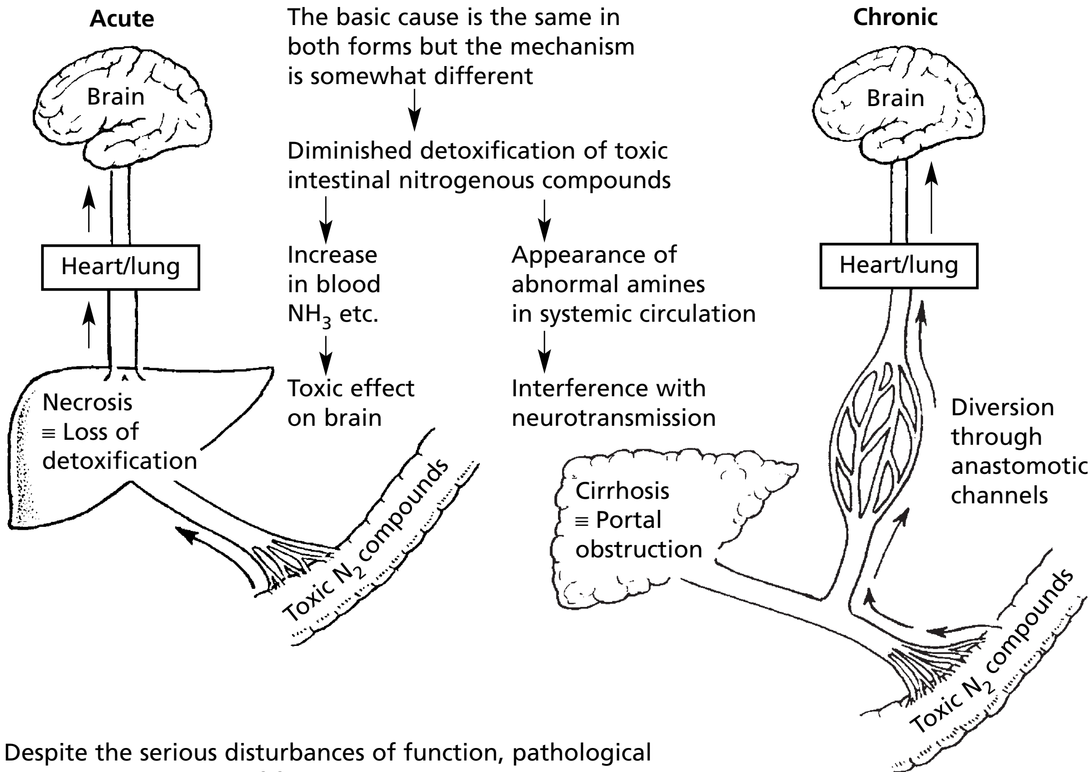


Jaundice
In acute liver failure, jaundice appears early and is related to the extent of liver damage. It arises as a result of lack of conjugation and excretion of bilirubin.

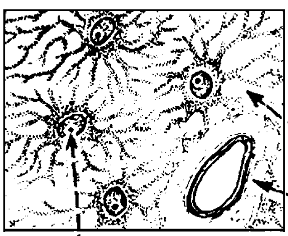
HEPATOCELLULAR FAILURE

HEPATIC ENCEPHALOPATHY

This term refers to the impaired mental state and neurological function due to liver failure. It takes the form of tremors, behavioural changes, convulsions, delirium, drowsiness and coma. In the acute form, severe symptoms such as convulsions, delirium and coma develop rapidly, while in chronic conditions milder changes are seen and coma is a late feature, unless a complication arises.



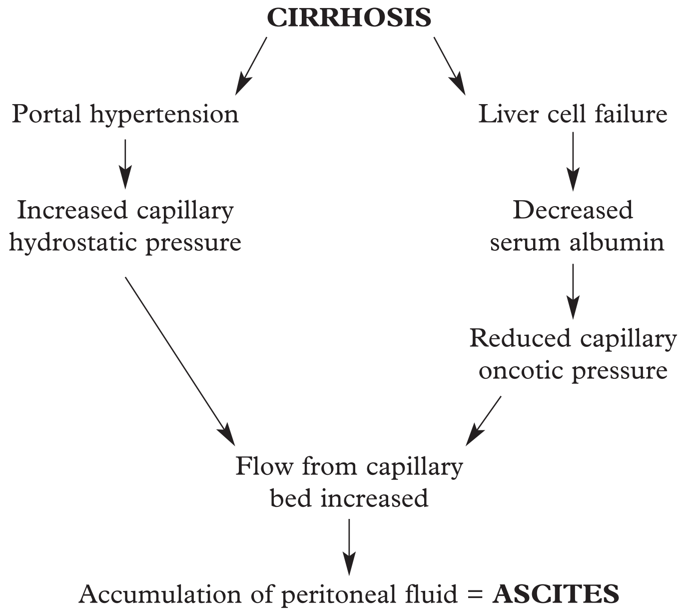
Despite the serious disturbances of function, pathological changes in the brain of fatal cases are surprisingly slight.



HEPATOCELLULAR FAILURE

HEPATOCELLULAR FAILURE (*continued*)

1. **ASCITES** is usually due to a combination of **portal hypertension** and **hepatocellular failure**.



2. **ANAEMIA** usually of normocytic/normochromic type (p.408) is common – splenomegaly may cause hypersplenism and pancytopenia (p.430)

3. **Metabolic disorders**

   (a) Reduced protein synthesis e.g. fibrinogen, prothrombin, factors V, VII, IX, X ⟶ bleeding diathesis.

   (b) Reduced liver glycogen storage ⟶ hypoglycaemia.

   (c) Reduced elimination of endogenous oestrogen ⟶ gynaecomastia, testicular atrophy and spider naevi (small skin capillary telangiectasia).

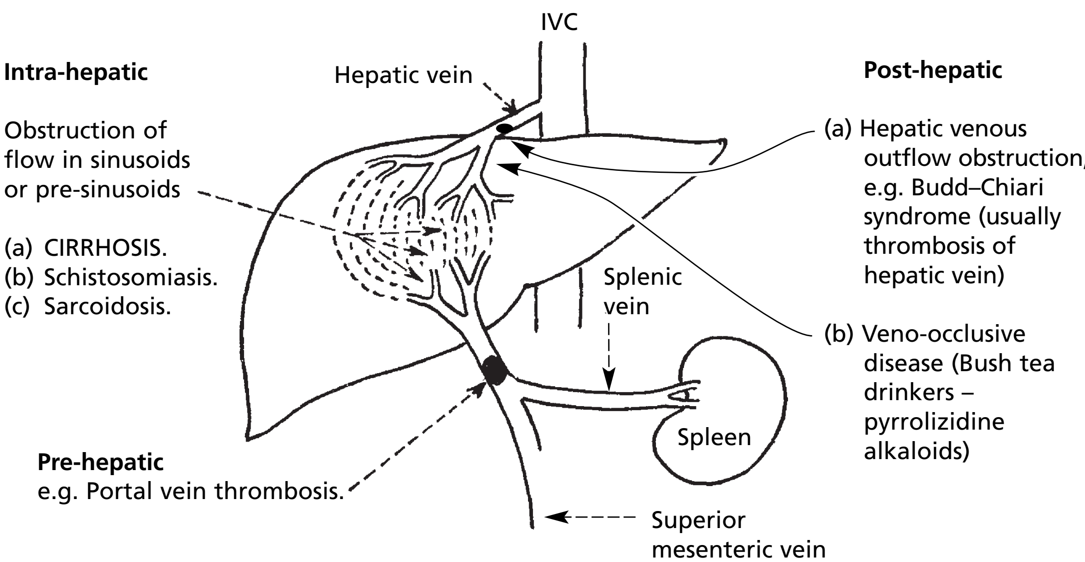
4. **Hepato-renal syndrome** is an important complication of a major haemorrhage from oesophageal varices.

Liver transplantation is increasingly used to treat acute and chronic hepatocellular failure, as well as some small hepatocellular carcinomas. As with other transplanted organs, acute and chronic rejection are seen.

PORTAL HYPERTENSION

In cirrhosis of the liver, **portal hypertension** is also important.

Causes
By far, the most important cause is cirrhosis, but there are many others broadly classified as 1. pre-sinusoidal, 2. intra-sinusoidal and 3. post-sinusoidal.

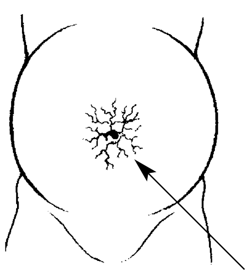


Effects
The main consequences are:

Portal hypertension

↓ Splanchnic congestion
- ↓ **Splenomegaly** ± hypersplenism
- ↓ **Ascites** ↑ aggravated by hypoalbuminaemia due to hepatocellular failure

↓ Porto-systemic shunting
- ↓ e.g. oesophageal varices ↓ **Haemorrhage**
- ↓ Blood flow bypassing liver ↓ Toxic effects, e.g. **encephalopathy** (p.353)

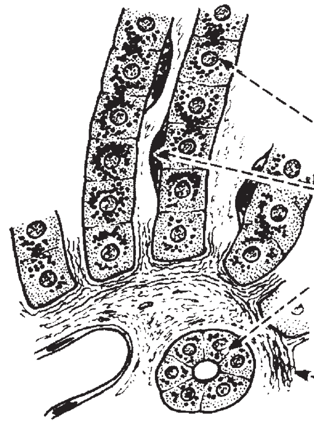


Simple clinical examination may show swollen abdomen due to ascites and caput medusae – engorged subcutaneous veins around the umbilicus.

METABOLIC DISORDERS AND THE LIVER

HAEMOCHROMATOSIS
Almost all cases are due to a mutation on chromosome 6, encoding the HFE protein which regulates iron absorption.
Although heterozygotes absorb excess iron, only homozygotes develop the disease.

EXCESS ABSORPTION OF IRON
↓
Deposition in parenchymal cells
↓ Pancreatic islets → DIABETES
↓ Myocardium → CARDIAC FAILURE
↓ Liver → Fibrosis → CIRRHOSIS



Note: In the skin, the iron is deposited mainly in the sweat glands: excessive melanin production in the epidermis explains the term 'bronzed diabetes' for these cases.

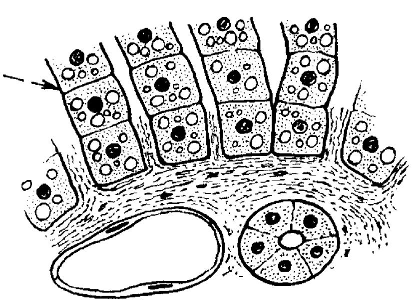
HAEMOSIDEROSIS – Excess dietary iron and repeated blood transfusions may overload the body iron stores but cause less liver damage.

WILSON'S DISEASE (HEPATO-LENTICULAR DEGENERATION)
A rare autosomal recessive condition (due to mutation of the ATP7B gene on chromosome 13 which encodes a copper transporting enzyme). This is characterised by accumulation of copper in the liver, brain (basal ganglia) and cornea (Kayser–Fleischer rings). Serum levels of caeruloplasmin (a copper binding protein) are reduced. The liver can show an acute hepatitis, chronic hepatitis or cirrhosis.

α_1-ANTITRYPSIN DEFICIENCY
This enzyme is a protease inhibitor (Pi) produced mainly by the liver. Reduced levels or activity of the enzyme (abnormal forms coded by allelic variants) may result in liver damage.

Liver disease is found in most **homozygotes** (PiZZ) and presents as neonatal hepatitis, chronic active hepatitis or cirrhosis. Heterozygotes are rarely badly affected.

The abnormal enzyme is not secreted by liver cells and accumulates as globules in the periportal hepatocytes.



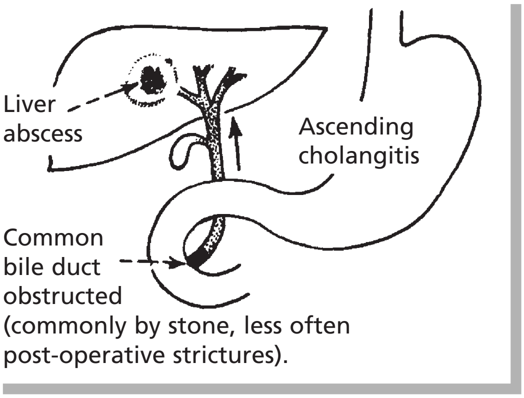
Note: α_1-antitrypsin deficiency is an important factor in the development of emphysema (p.261).

INFECTIONS

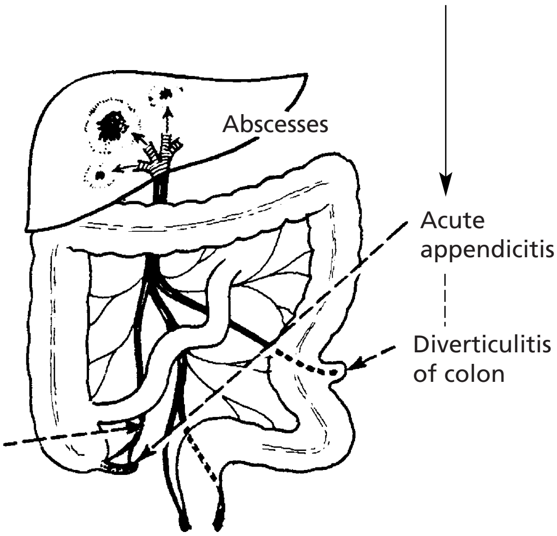
PYOGENIC INFECTIONS

These are now much less common due to the use of antibiotics. Abscess of the liver, usually due to coliforms, occurs mainly in two conditions:

1. **Ascending cholangitis**



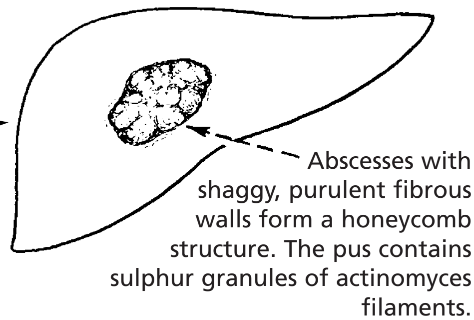
2. **Suppurative pylephlebitis**
   This arises from suppurative lesions in the abdominal cavity such as:



Inflammation
↓
Septic thrombosis of associated veins
↓
Septic emboli in portal veins or spreading pylephlebitis
↓
Liver abscess

ACTINOMYCOSIS

The appendix is usually the site of the initial lesion. Spread to the liver is via the portal blood but may be direct. The liver lesion is characteristic of *Actinomyces israelii* infection.



TUBERCULOSIS

This is rare. Miliary tubercles may be seen in generalised infection.

HEPATIC GRANULOMAS

Granulomas are also common in sarcoidosis and may also occur in brucellosis, histoplasmosis and primary biliary cirrhosis, among many other causes.

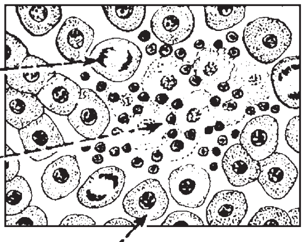
INFECTIONS

SPIROCHAETAL INFECTIONS

Three spirochaetal infections can involve the liver.

1. **Leptospira icterohaemorrhagica (Weil's Disease)**

This organism is transmitted from rats to man, especially these working in wet conditions, e.g. in sewers and abbatoirs. The disease is characterised by fever, jaundice, haemorrhage into various organs, e.g. lungs, kidneys, and renal damage. The liver lesion is characteristic. Death may occur from intrapulmonary haemorrhage or renal failure.

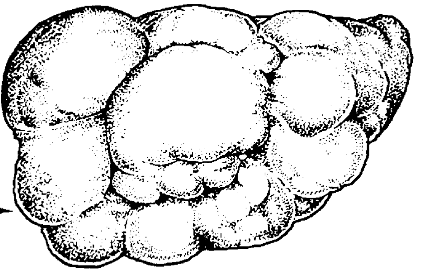


2. ***Treponema pallidum***

Syphilitic lesions of the liver are now uncommon in the UK.

(a) *Congenital infection.* This usually produces a diffuse interstitial fibrosis which isolates individual liver cells and causes ischaemic atrophy. It is accompanied by a striking mononuclear infiltration and tiny areas of coagulative necrosis – miliary gummas. Spirochaetes are often plentiful.

(b) *Acquired infection.* Lesions can occur in the secondary and tertiary stages. In the secondary stage, a diffuse, inflammatory reaction with miliary gummas can occur. Large gummas may be seen in tertiary syphilis. Gross scarring with distortion follows healing – hepar lobatum.



3. **Borrelia**

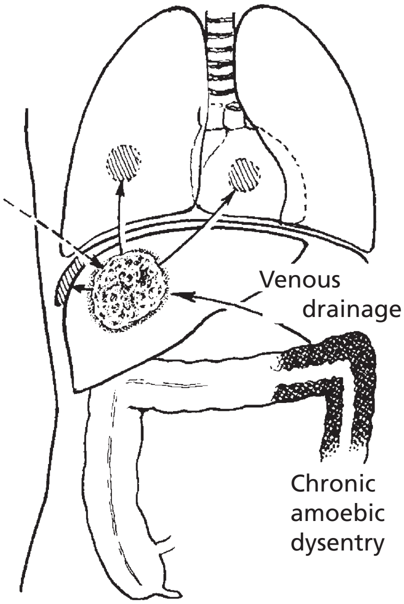
Borrelia occur in many parts of the world and several species exist, e.g. *B. recurrentis*. They are transmitted by lice and ticks from animals acting as reservoirs, especially rodents. The infections produce peri-venular necrosis of the liver. Jaundice may be severe and liver failure can result in death.

INFECTIONS

PROTOZOAL DISEASES

Amoebic 'abscess'

This is a complication of amoebic dysentery due to *Entamoeba histolytica*. The 'abscess' is usually single, in the upper right lobe of liver. An irregular fibrous wall encloses off necrotic liver cells, debris and red cells. Amoebae may be found in the inner wall. It may remain localised or track through the diaphragm into the lung, pleural or pericardial cavities.



Malaria

On initial infection, the parasites develop within the hepatocytes but produce little damage. In chronic malaria, red cells containing parasites are engulfed by Kupffer cells which become hyperplastic and contain brown malarial pigment.

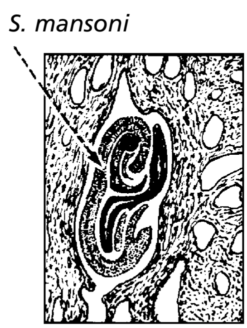
Kala-azar (Visceral Leishmaniasis)

The liver is enlarged due to hyperplasia of the Kupffer cells which phagocytose many Leishman–Donovan bodies, the protozoan responsible.

METAZOAL DISEASES Trematodes (flukes)

Schistosomiasis (Bilharzia)

S. mansoni is common in Egypt and other parts of Africa. *S. japonicum* is found in China, Japan and the Philippines. Both infections involve the liver.

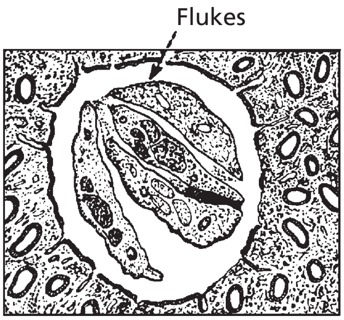


The schistosomes colonise the intestinal tract. They invade the intestinal veins; ova are released into the blood stream and embolise the portal venules of the liver. There is a focal granulomatous reaction which may lead to extensive portal fibrosis without cirrhosis. Portal hypertension can result with its associated complications.

INFECTIONS

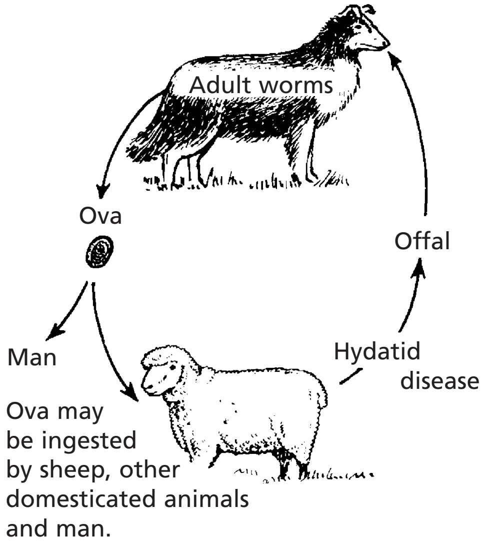
METAZOAL DISEASES (*continued*)

Two other varieties of fluke disease exist — clonorchiasis (Chinese fish fluke) and fascioliasis (sheep fluke). Both produce an ascending cholangitis. Clonorchiasis can cause biliary obstruction and marked proliferation of bile ducts. Cholangiocarcinoma may develop. Infestation in both cases is due to eating raw or undercooked food.



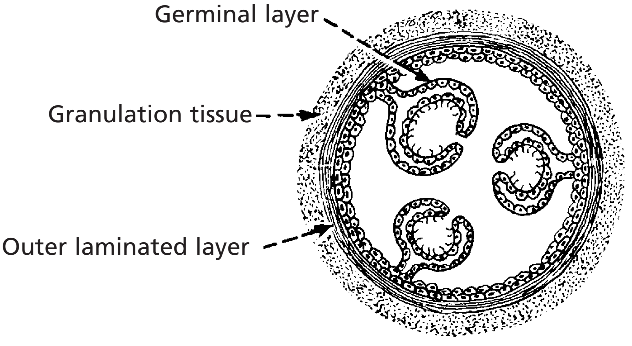
Hydatid disease

This condition is caused by the embryos of *Echinococcus granulosus*, a small tapeworm. The disease is caught by close contact with animal reservoirs especially sheep and dogs. It is commonest in Australia, New Zealand, South America and the Middle East.



Digestion of the chitinous membrane by gastric juice releases the ova which invade the intestinal veins and reach the liver. Sometimes they pass into the systemic circulation and cysts form in the lungs, muscles, kidneys, spleen or brain.

The cyst may be very large, usually multilocular, due to budding of daughter cysts.



Serological tests are positive in half of cases

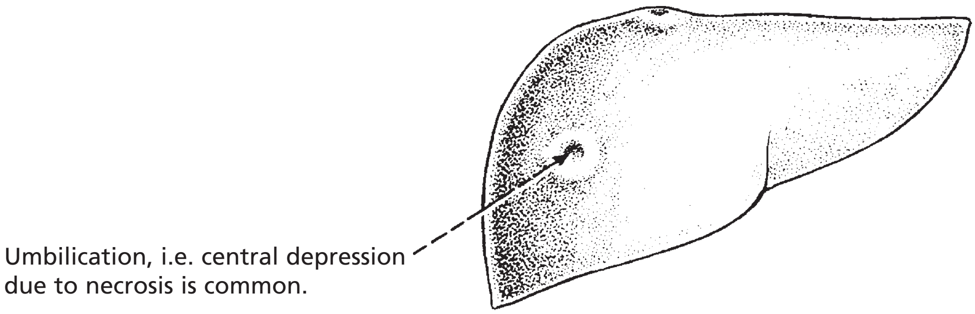
TUMOURS OF THE LIVER

PRIMARY BENIGN TUMOURS

1. **Cavernous haemangioma.** This is the commonest type. It forms a dark purple, sharply demarcated geometric patch on the liver surface and consists of dilated blood vessels.
2. **Liver cell adenoma.** These small tumours are rare and are associated with the use of the contraceptive pill and anabolic steroids. They consist of normal liver trabeculae without normal portal tracts. Intraperitoneal bleeding may occur.
3. **Bile duct adenoma.** These small tumours are usually incidental findings at laparotomy. They consist of tiny bile duct structures set in loose connective tissue. Occasionally bile duct cystadenomas form large tumours.

SECONDARY TUMOURS

The liver is by far the most frequent site of secondary tumour deposits and these are far commoner than primary liver tumours. The common primary sites are the gastrointestinal tract, the lung and breast. Melanoma, leukaemic infiltration and involvement by lymphoma are also often seen.



The metastases often grow rapidly and are frequently the main cause of death. An exception is metastatic carcinoid tumour which grow slowly over a period of years (p.334).

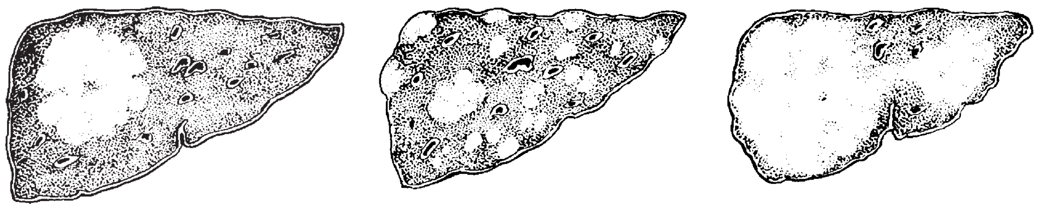
Increasingly, metastases, e.g. from colorectal cancers, are treated by radio frequency ablation or surgical resection.

PRIMARY CARCINOMA OF LIVER

HEPATOCELLULAR CARCINOMA (HCC)

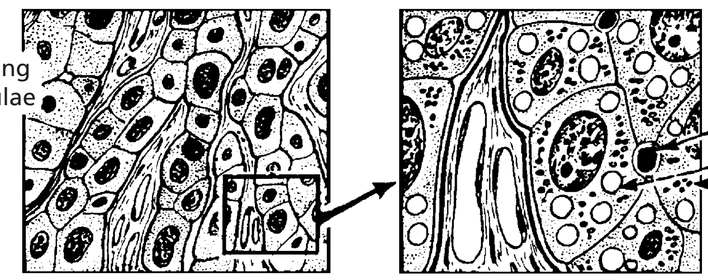
This, the commonest primary malignancy of the liver, is unusual in Western Europe, but is very common in Africa and South-East Asia. Males are particularly affected.

Three main types of growth are described:



In all three forms the liver is often cirrhotic (80%) (particularly in the West).

Histological structure: The cells grow in columns resembling normal liver.



Spread

In addition to diffuse growth within the liver, **invasion of hepatic veins** occurs early and there may be metastases to lung, bone and also the draining lymph nodes.

The proximate **cause of death** may be (i) liver failure, (ii) the complications of portal hypertension (especially in cirrhotic patients) and (iii) massive intraperitoneal haemorrhage.

Systemic manifestations include hypoglycaemia, hypercalcaemia and polycythaemia (due to production of erythropoietin).

Diagnosis

Liver biopsy is usually required. High levels of alpha-fetoprotein (normally produced in the fetal liver), >500 μg/l are strong supportive evidence (not all tumours produce this protein). This can be demonstrated in tumour cells by immunostaining. In-situ hybridisation can show mRNA for albumin in αFP-negative tumours.

Increased levels of αFP are also seen in:
1. Cases of testicular teratoma (p.526) or ovarian yolk sac tumour (p.512).
2. Liver damage (the levels are much lower).

PRIMARY LIVER CELL TUMOURS

HEPATOCELLULAR CARCINOMA (HCC) (*continued*)

Aetiology

The aetiological agents vary in low and high incidence areas.

WESTERN EUROPE

ALCOHOLIC LIVER DISEASE

Also chronic active hepatitis including HBV + HCV, haemochromatosis

SE ASIA and AFRICA

HEPATITIS B + C VIRUSES

Aflatoxins (aspergillus flavus toxins)

In a minority of cases **no cirrhosis** is found

↓

CIRRHOSIS

↓

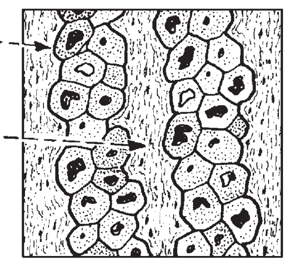
HEPATOCELLULAR CARCINOMA

FIBROLAMELLAR CARCINOMA

This uncommon variant (<5%) occurs especially in young adults. It is important because the prognosis is much better following surgical resection.

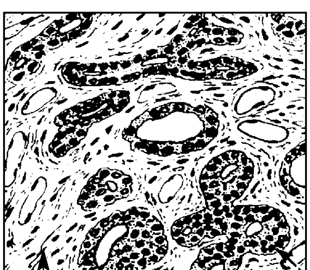
Histologically

Large polygonal tumour cells form trabeculae separated by fibrous stroma



Other differences from conventional HCC are:
(1) Usually no cirrhosis
(2) AFP not raised
(3) Hepatitis B infection rare – aetiology uncertain.

CHOLANGIOCARCINOMA



Fibrous stroma

Cells resemble bile duct epithelium

These tumours arise from bile ducts at both intra- and extrahepatic sites.

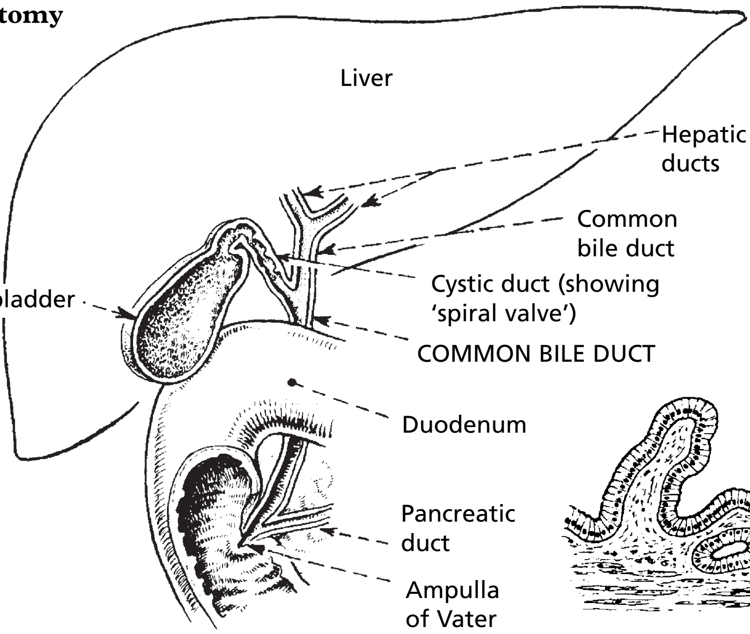
They are usually adenocarcinomas: some show excess mucus secretion and evoke a dense fibrous response.

Cirrhosis is rarely present.

There is an increased incidence in association with ulcerative colitis and primary sclerosing cholangitis, and in the Far East there is a clear association with liver fluke (clonorchis) infestation.

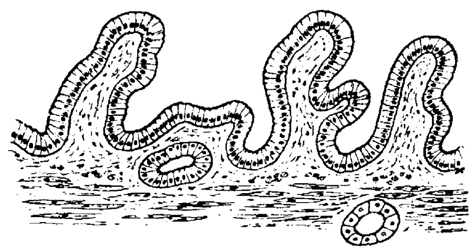
GALLBLADDER AND BILE DUCT – ANATOMY

Anatomy



Histology
(Gallbladder)

1. The surface is lined by tall columnar cells.
2. Mucus secreting glands near the neck.
3. Longitudinal, circular and oblique muscle bundles.

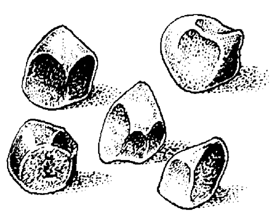


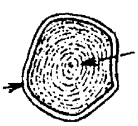
The function of the gallbladder is to concentrate and store bile.

GALLSTONES

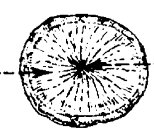
Gallstones are the principal cause of gallbladder disease and its consequences.
There are 3 main types:

1. **Mixed stones** account for 80% of all gallstones. They are **multiple** and **faceted** due to contact with one another.





2. **Cholesterol stone** – is usually solitary, oval and up to 2–3 cm in length. They are associated with excessive cholesterol in the bile.



3. **Bile pigment stones** – are multiple and are usually due to chronic haemolysis with excess bilirubin production.



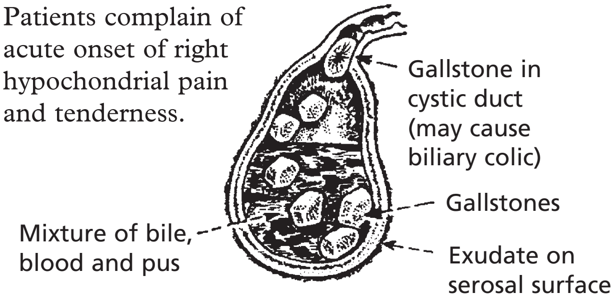
GALLSTONES

Clinical manifestations and complications

Many patients are asymptomatic or have only mild dyspepsia; others develop symptomatic complications.

1. **ACUTE CHOLECYSTITIS**

Patients complain of acute onset of right hypochondrial pain and tenderness.



Progress

Mild cases → resolution

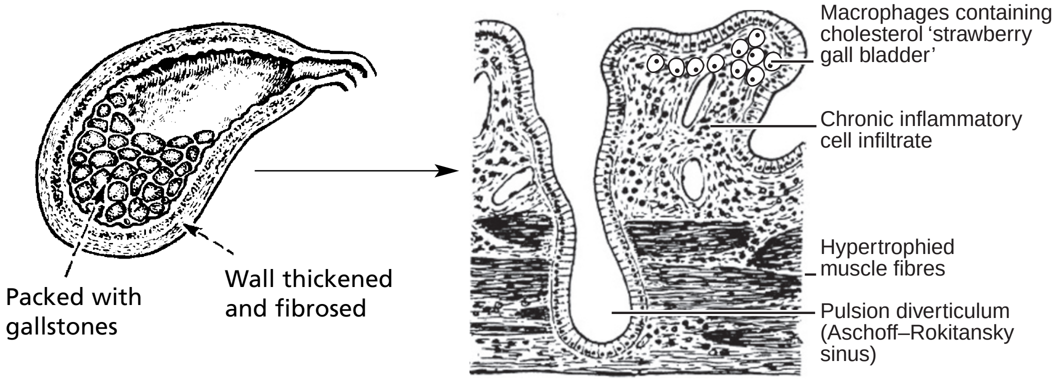
Recurrent attack → chronic cholecystitis

Severe cases → perforation → peritonitis

Severe cases → Empyema (distended bag of pus)

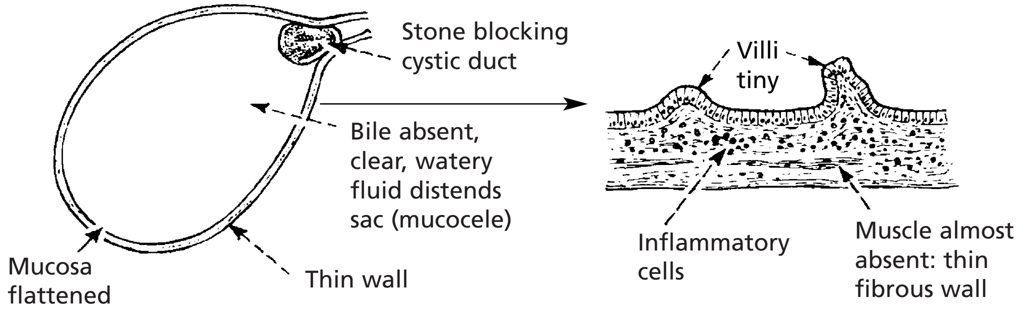
2. **CHRONIC CHOLECYSTITIS**

In the majority of cases the symptoms are of vague 'indigestion ', intolerance of fatty foods and vague right hypochondrial pain: in some cases there is a history of acute attacks.



3. **MUCOCELE** – can occur when the cystic duct is blocked.

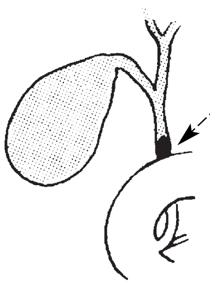
This occurs when there has been long-standing obstruction of the cystic duct.



GALLSTONES

GALLSTONES (*continued*)

4. **COMMON BILE DUCT GALLSTONES**

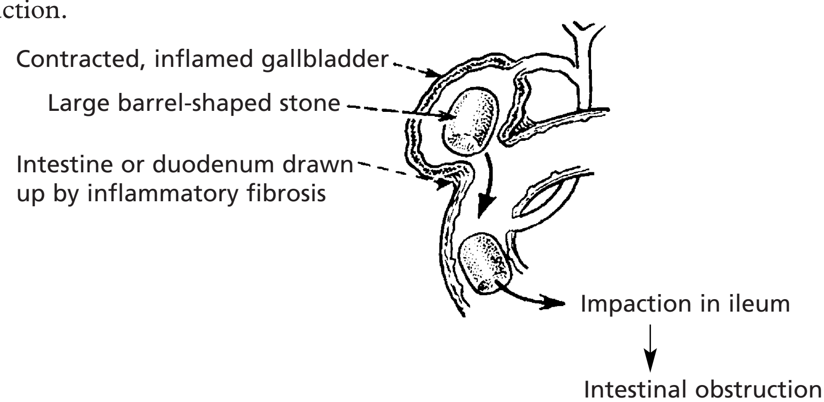


Stone in the COMMON BILE DUCT → OBSTRUCTION of BILE FLOW

- → OBSTRUCTIVE JAUNDICE (often intermittent) → Very rarely secondary biliary cirrhosis (p. 350)
- → ASCENDING INFECTION → CHOLANGITIS
- → ACUTE PANCREATITIS (p.370)

Note: In addition to jaundice, persistent skin itching, due to retention of bile salts, may occur.

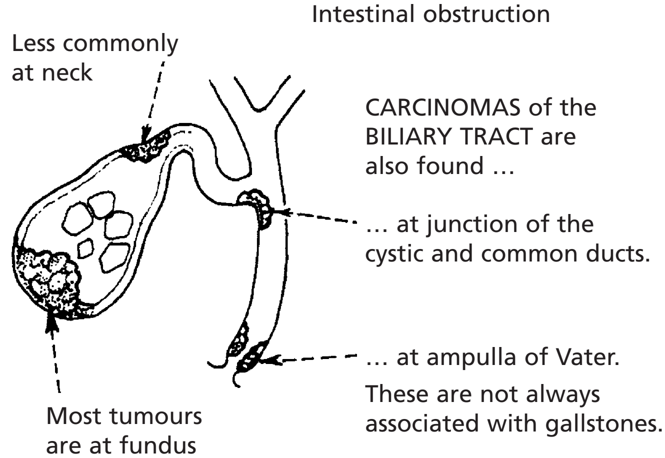
5. **GALLSTONE ILEUS**
Very rarely a stone may ulcerate through the gallbladder into the intestine and cause obstruction.



6. **CARCINOMA of the GALLBLADDER**
This is uncommon, but almost always associated with gallstones.

Most cases are adenocarcinomas which spread directly to the liver.

Very occasionally squamous cancers develop.

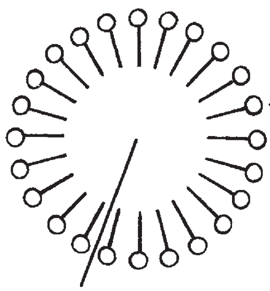


GALLSTONES – AETIOLOGY

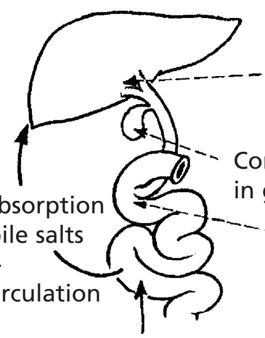
Although gallstones are found in 10–20% of the population, the prevalence increasing with age, the exact mechanisms of their formation remain incompletely understood. Risk factors include (a) female gender, (b) obesity, (c) pregnancy, (d) drugs such as the cholesterol lowering drug clofibrate now seldom used and (e) gastrointestinal disease, e.g. Crohn's disease.

The principal constituents of bile are **cholesterol, phospholipids** and **bile acids** (cholic acid and chenodeoxycholic acid).

The **stability of cholesterol** depends on adequate amounts of bile acids. Micelles are formed.



Their **enterohepatic circulation** is essential to maintain adequate concentrations of bile salts.



The ratio of cholesterol:bile salts is very important.

Increased biliary cholesterol secretion
or
Increased cholesterol synthesis
or
Decreased bile salts (e.g. in Crohn's disease)

} Ratio increased $\frac{\text{Cholesterol} \uparrow}{\text{Bile salts} \downarrow}$ → Precipitation of CHOLESTEROL → NUCLEATION (formation of tiny stones)

↓

Progressive accumulation of cholesterol and pigment

↓

ENLARGING STONES

Stones often lead to infection: it is likely that infection promotes further stone production.

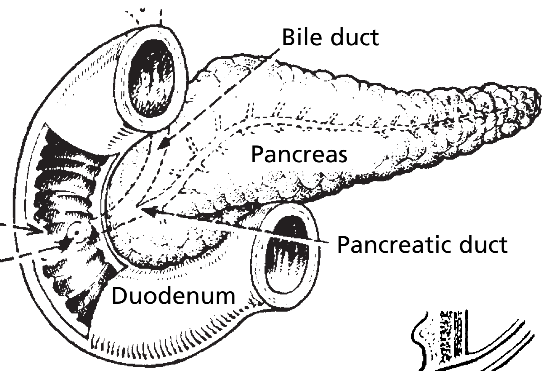
These mechanisms are responsible for cholesterol and mixed stones. Pigment stones are seen in haemolytic anaemia, but also in relation to infection, e.g. of *E. coli*. The mechanisms are poorly understood.

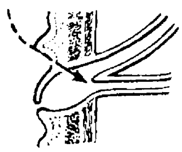
PANCREAS

The exocrine glandular portion of the pancreas produces digestive secretions which are released into the second part of the duodenum.

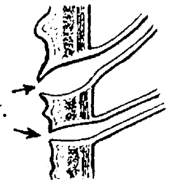
Anatomical variations occur in this region.

Commonly the pancreatic and bile ducts fuse as they enter the ampulla of Vater …



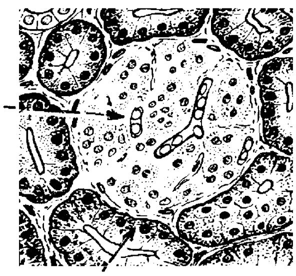


…but sometimes they enter the duodenum separately.



Microscopically, the exocrine tissue is similar to salivary glands.

In addition, foci of endocrine islet tissue occur throughout the pancreas (islets of Langerhans)



Exocrine secretory granules

Function: The exocrine pancreas produces an alkaline secretion containing digestive enzymes.
Sodium bicarbonate – gives a pH 7.5–8.0
Amylase – splits starches. Lipase – digests lipids.
Trypsinogen } converted to active proteolytic
Chymotrypsinogen } enzymes, trypsin, chymotrypsin.

The islet tissue produces insulin and glucagon (and other neuropeptides). Disorders of the islets, e.g. diabetes, are discussed on page 637.

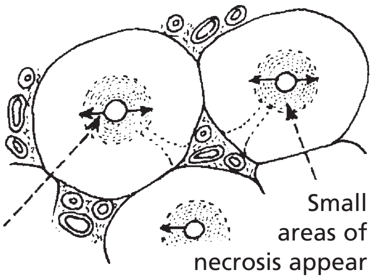
There is evidence that mild pancreatitis is not uncommon but, in a significant number of cases, progression to a severe fatal disease occurs. Clinically, there is an acute abdominal emergency with pain and shock.

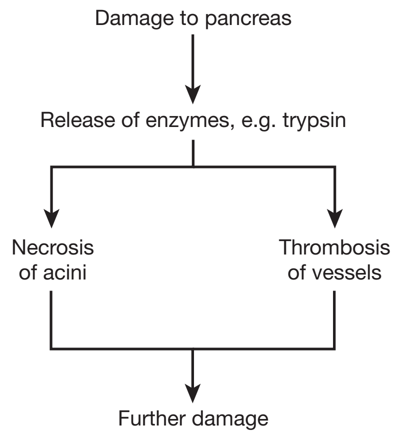
The essential pathological changes are due to tissue necrosis caused by the action of liberated enzymes on the pancreatic tissues. The severity of the lesion depends on the amount of enzyme set free, the distance it diffuses, anti-proteolytic factors and the structures affected.

ACUTE PANCREATITIS

Early changes are seen in centre of the lobules.

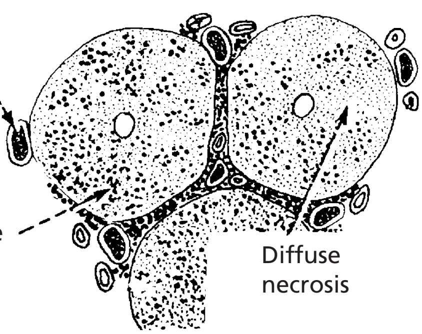
Periductal necrosis – in the centre of each affected lobule.

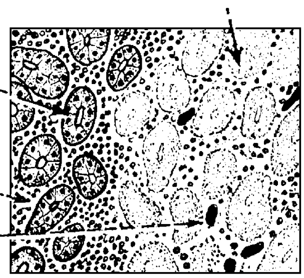




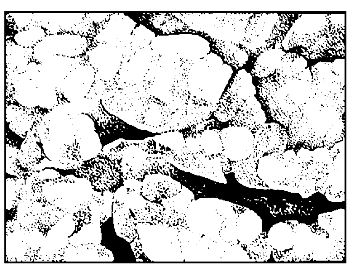
Unless this damage is inhibited by α_1 antitrypsin and α_2 macroglobulins from the blood and pancreatic secretory trypsin inhibitor, inflammation progresses to:

PANLOBULAR PANCREATITIS





Release of enzymes beyond the pancreas gives fat necrosis of the omentum.



ACUTE PANCREATITIS

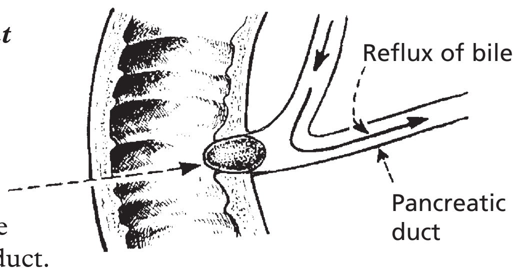
In acute pancreatitis, acute inflammation is associated with necrosis of pancreatic acini and fat.

Patients present with abdominal pain and vomiting with a differential diagnosis of perforated duodenal ulcer. A serum level of amylase >1200 IU/L and serum lipase >160 IU/L confirms the diagnosis. Many cases are mild, but a third of severe cases have a mortality of 50%.

Aetiology
Two factors are important: 1. gallstones and 2. alcohol.

Gallstones
Between 40 and 60% of all cases of severe pancreatitis are associated with gallstones. Recurrent attacks are common.

Bile reflux is the initiating event
In most patients, the bile duct and pancreatic duct have a common entrance to the ampulla of Vater. Stones around 3 mm in diameter passing down the bile duct can, by blocking the ampulla, cause reflux of bile along the pancreatic duct.



Alcohol
Acute pancreatitis is common in alcoholics and the incidence of this association is directly related to the consumption of alcohol by the local population.

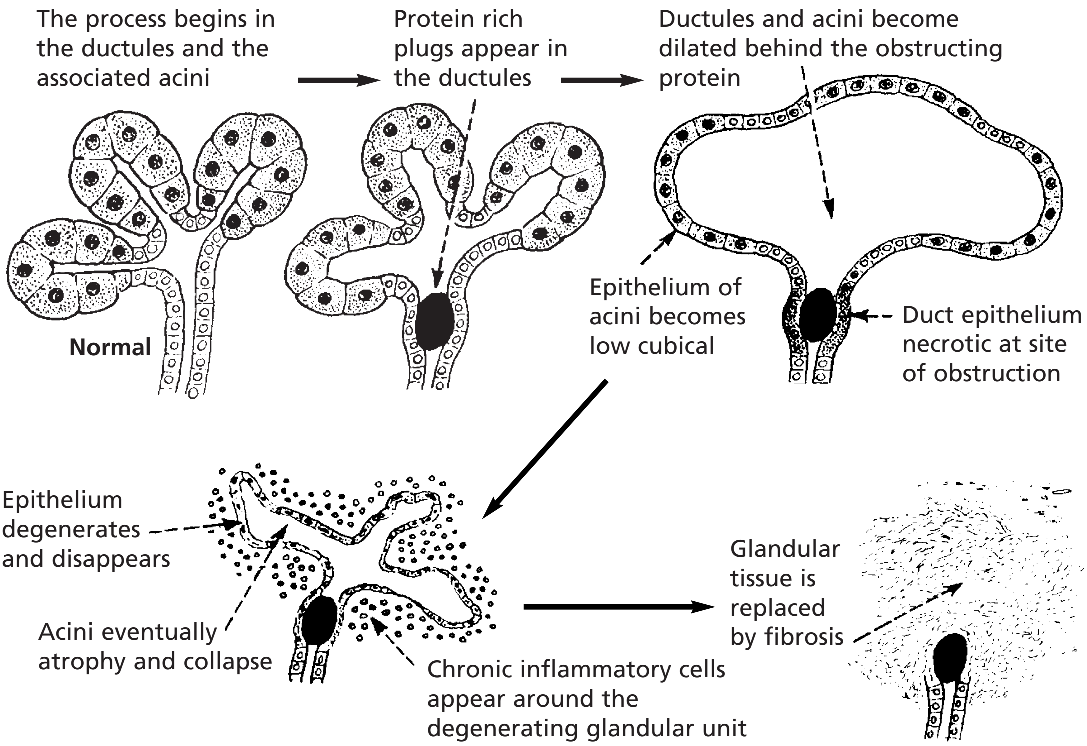
The precise mechanisms are poorly understood, but include:
- Ampullary spasm.
- Plugging of ducts by inspissated secretion.
- Toxic effects on acinar cells.

Other causes include:
- Hereditary forms, with mutations of the cationic trypsinogen gene (PRSS-1).
- Trauma, including surgery.
- Viruses, e.g. mumps, coxsackie B.
- Hypercalcaemia, e.g. in hyperparathyroidism.
- Drugs, e.g. steroids.

Complications
(i) Shock is the major cause of death.
(ii) Recurrent attacks may lead to chronic pancreatitis.
(iii) Collections of fluid may be surrounded by fibrous tissue – pancreatic pseudocyst (p.372).

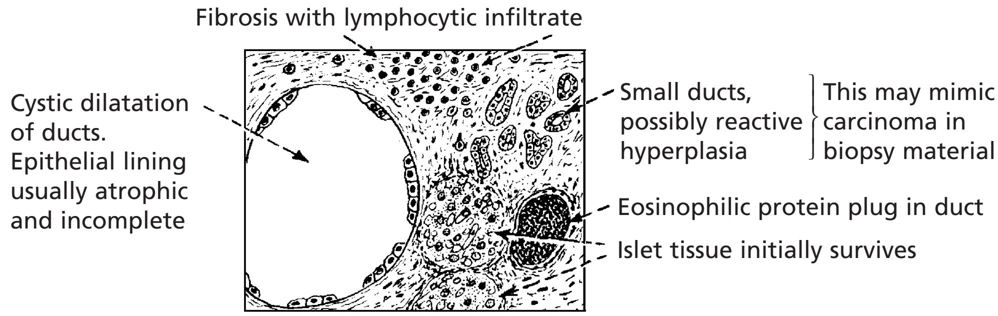
CHRONIC PANCREATITIS

Chronic pancreatitis predominantly affects alcoholics.



The change is focal. More and more protein plugs form, some in larger ducts. Obstruction of these may lead to production of cysts.

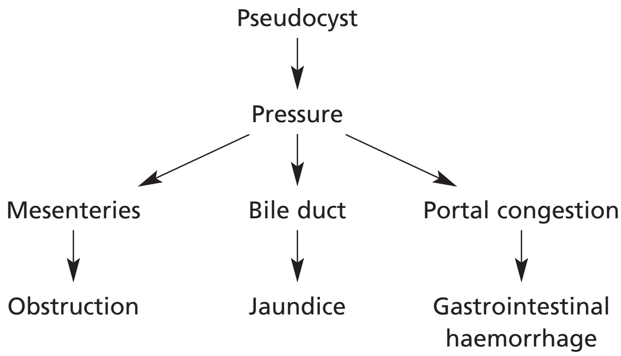
Ultimately, a large proportion of the exocrine tissue is destroyed.



CHRONIC PANCREATITIS

With progress of the disease, two other developments take place:

1. *Calcification.* This occurs mainly in the protein plugs in the ducts, resulting in the formation of calculi.
2. *Rupture of the duct cysts into the surrounding tissues.* A granulation tissue reaction is set up with formation of a pseudocyst. The result depends on the site of the pseudocyst.



Rupture into the peritoneal cavity causes ascites, frequently haemorrhagic.

Progressive destruction of the parenchyma with fibrosis may ultimately convert the pancreatitis into a thin hard cord.

Effects
Patients typically complain of abdominal pain.

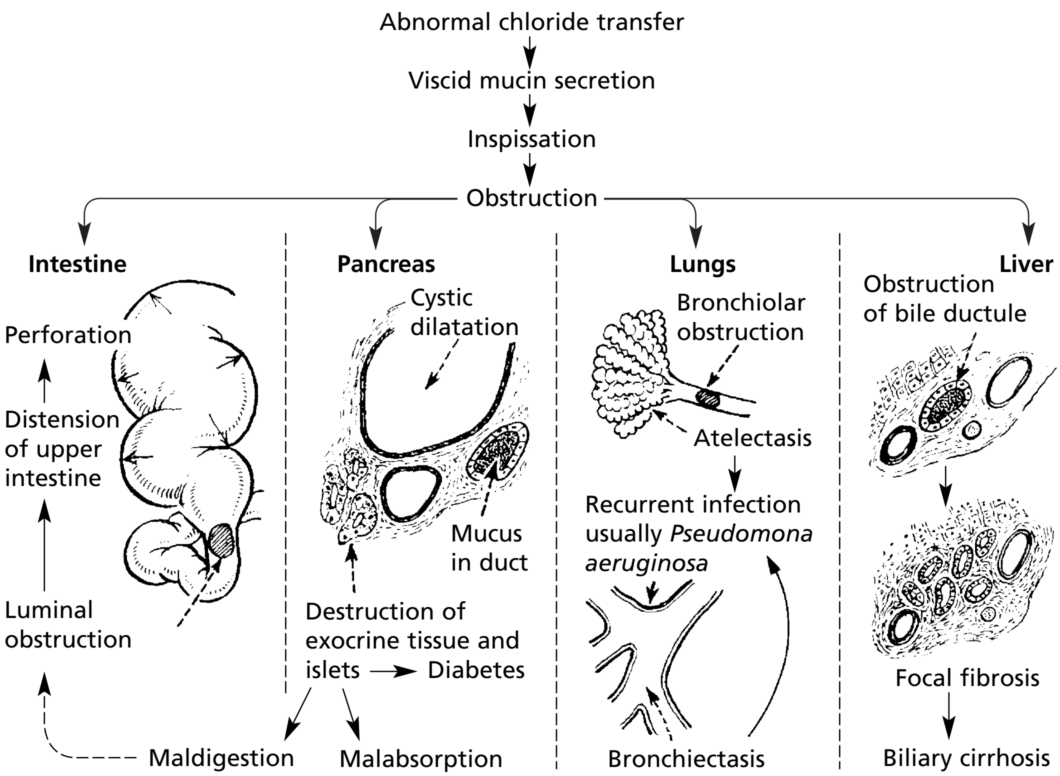
Apart from the complications due to cyst rupture, destruction of pancreatic tissue may lead to:

1. Insufficiency of exocrine secretion → steatorrhoea and wasting.
2. Diabetes mellitus. 30% of patients eventually develop this due to destruction of islet tissue.

Aetiology
1. The main factor in 75% of cases in Western civilisation is alcohol. Patients have generally consumed more than 150 g daily over a long period of time.
2. Some cases may follow recurrent attacks of acute pancreatitis.
3. A peculiar type of chronic ‘tropical’ pancreatitis occurs in Africa and South East Asia. It is related to chronic malnutrition with particular deficiency of protein, from infancy. Extensive calcification of the pancreatic tissue occurs. It has been suggested that there is a genetic predisposition to the disease.
4. Genetic causes are increasingly recognised as in acute pancreatitis.

CYSTIC FIBROSIS (Mucoviscidosis)

This is a common autosomal recessive inherited disease due to genetic mutation on chromosome 7; a high percentage (about 4%) of the population are carriers.
The gene involved is called cystic fibrosis transmembrane conductance regulator (CFTR). Its essential function is the control of the transfer of chloride across cell membranes. Many mutations of the gene have been recorded, each being responsible for subtle variations in the evolution of the disorder.
All the exocrine secretory tissues are affected to some extent: the clinical features vary according to which organs are severely affected – pancreas, bronchi, bowel, biliary tree, testis.



Clinical features

Neonatal

Intestinal obstruction (meconium ileus) may lead to intestinal perforation and fatal peritonitis.

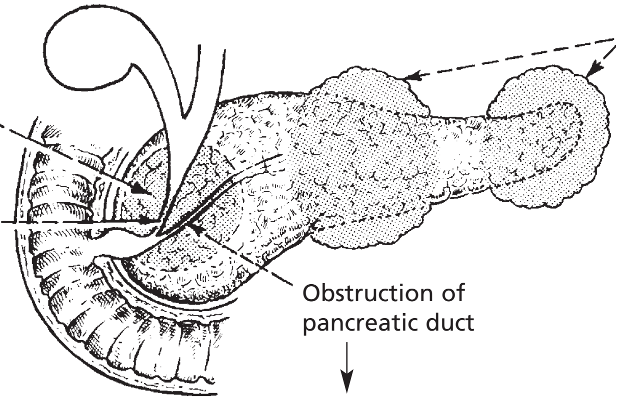
Childhood

There is failure to thrive due to maldigestion and malabsorption, and steatorrhea is common – all features of pancreatic insufficiency. Recurrent episodes of pneumonia often lead to death in early adult life. Lung transplantation and gene therapy offer hope of improved survival. Liver lesions develop later.
Sodium chloride levels are raised in sweat detected in the ‘sweat test’. Genetic screening is now available.

TUMOURS OF PANCREAS

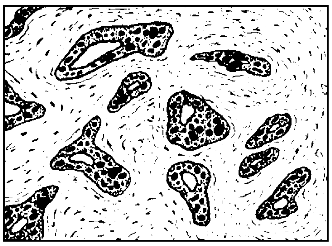
Benign tumours of the pancreas such as cystadenomas are rare. They may produce symptoms due to pressure on other structures.

CARCINOMA



Local spread and/or distant metastases are found in 85% of cases at the time of diagnosis and the 5 year survival rate is 3–5%.

The tumour arises from the duct epithelium and in almost all cases it is an adenocarcinoma. Papillary cystadenocarcinoma, adenosquamous carcinoma and giant cell carcinoma are forms occasionally encountered.



Tumours in the body and tail are commonly larger than tumours of the head, probably due to later diagnosis in the relative absence of symptoms.

Thrombosis of unknown cause and at distant sites (thrombophlebitis migrans, p. 236), e.g. femoral vein, may occur.

Aetiology

1. Pancreatic carcinoma is most frequent in males in the 5th–7th decades.
2. There is a statistical association with alcohol, cigarette smoking, a diet high in fat and carbohydrate and chronic pancreatitis.
3. In the U.S.A., the incidence is higher in the black population and a similar situation is true of the Maoris in New Zealand.

Endocrine Tumours are described on page 641.

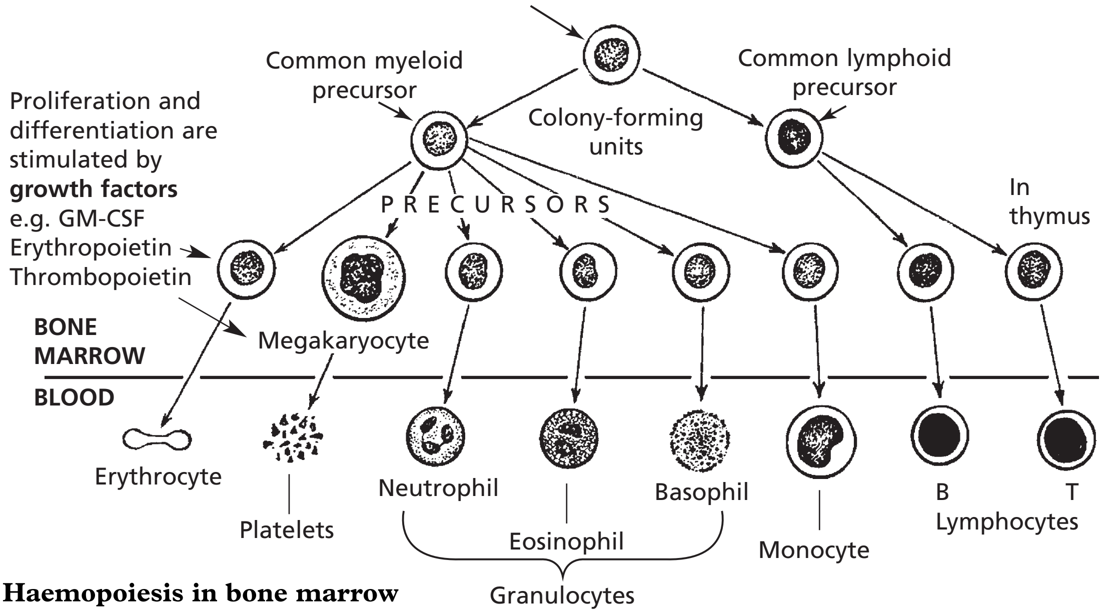
CHAPTER 11

HAEMOPOIETIC AND LYMPHO-RETICULAR TISSUES

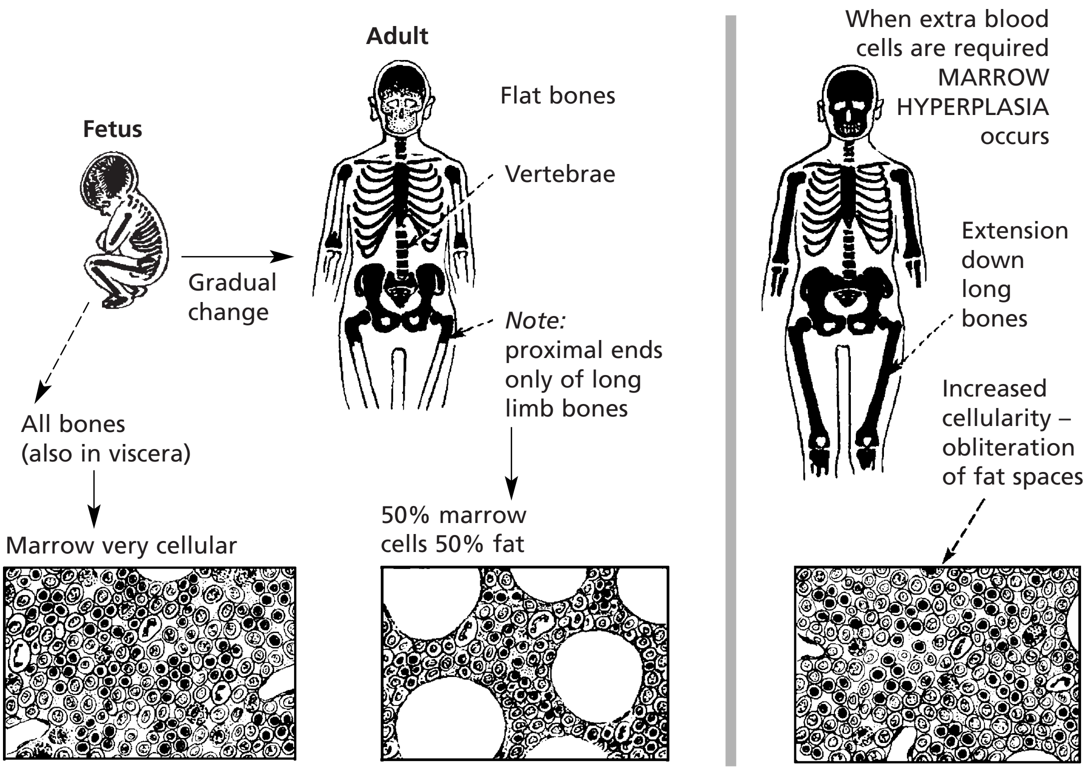
HAEMOPOIESIS

The derivation of blood cells

In the **bone marrow** a '**pluripotent**' **stem cell** gives rise to **all blood cells.**



Haemopoiesis in bone marrow



HAEMATOLOGY – LABORATORY TESTS

Investigation of blood diseases depends on examination of 1. PERIPHERAL BLOOD and 2. BONE MARROW.

1. PERIPHERAL BLOOD

Blood count: this is normally done by sophisticated electronic machines.
The main parameters are:

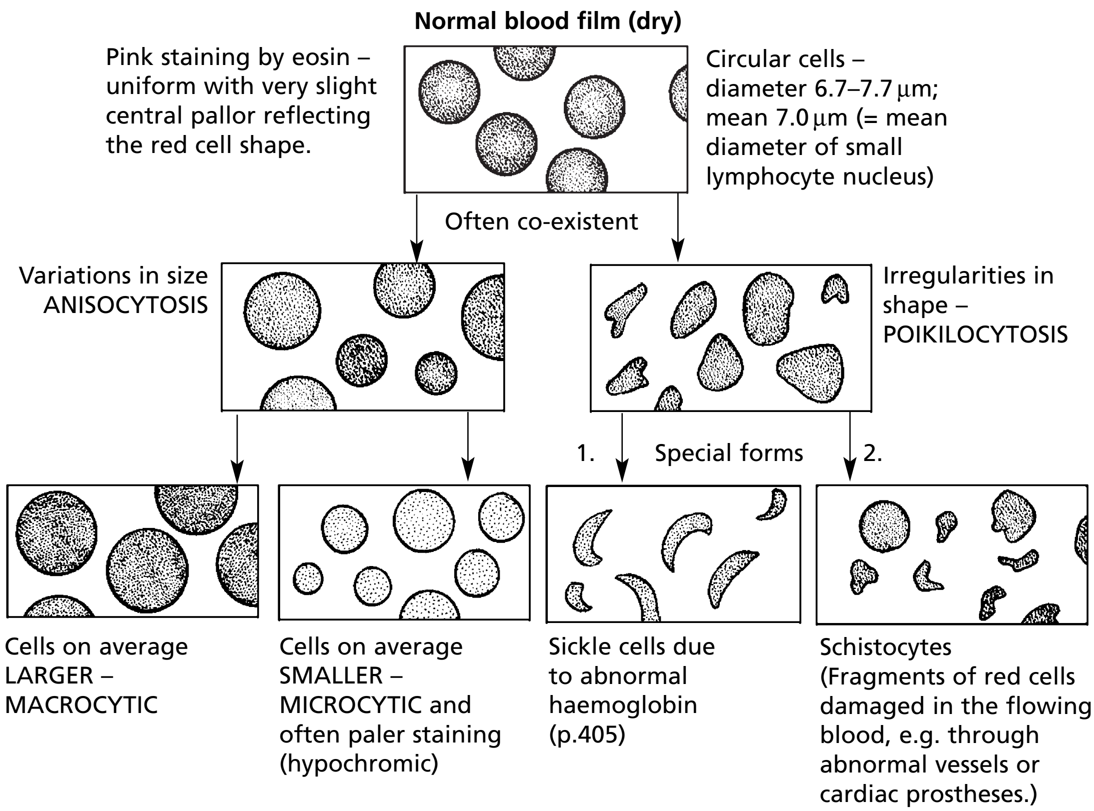
(i) **HAEMOGLOBIN (Hb) CONCENTRATION** (g/dl whole blood)
Normal values: Male 15.5±2.5: Female 14.0±2.5

(ii) **CELL COUNT**
Red Cell count: Males $5.5 \pm 1.0 \times 10^{12}$/l.
Females $4.8 \pm 1.0 \times 10^{12}$/l.
White Cell Count: $4–11 \times 10^{9}$/l.
Neutrophils – $2.0–7.5 \times 10^{9}$/l.
Lymphocytes – $1.5–4.0 \times 10^{9}$/l.
Monocytes – $0.2–0.8 \times 10^{9}$/l.
Eosinophils – $0.04–0.4 \times 10^{9}$/l.
Basophils – $0.01–0.1 \times 10^{9}$/l.
Platelets – $150–400 \times 10^{9}$/l.

(iii) **MEAN RED CELL VOLUME (MCV)**
Normal – 85±8 fl (femtolitres)

Also measured are:
MEAN CELL HAEMOGLOBIN
Normal = 29.5±2.5 picograms.
MEAN CELL HAEMOGLOBIN CONCENTRATION (MCHC)
Normal = 33±3 g/dl.

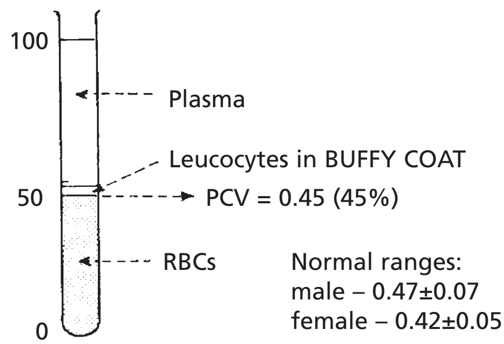
BLOOD FILM – stained by a Romanowski method.



HAEMATOLOGY – LABORATORY TESTS

Another useful test is the measurement of the **PACKED CELL VOLUME (PCV)** or haematocrit.

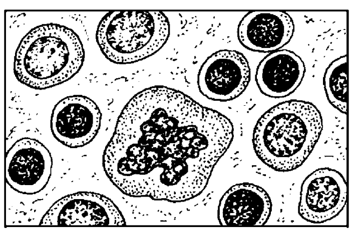
This is obtained by centrifuging anticoagulated whole blood in a haematocrit tube.



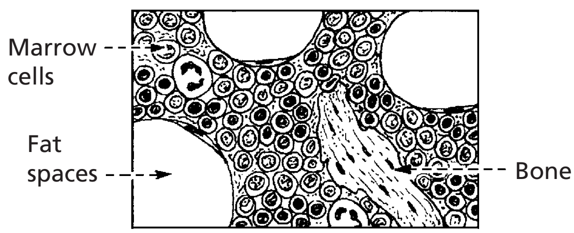
2. **BONE MARROW EXAMINATION**

Examination of bone marrow is important in explaining abnormalities of the peripheral blood.

In the past, aspiration of marrow from the sternum was commonly performed. Now the posterior iliac crest is used – it is safer and allows marrow to be **aspirated** and a **trephine biopsy** to be taken.



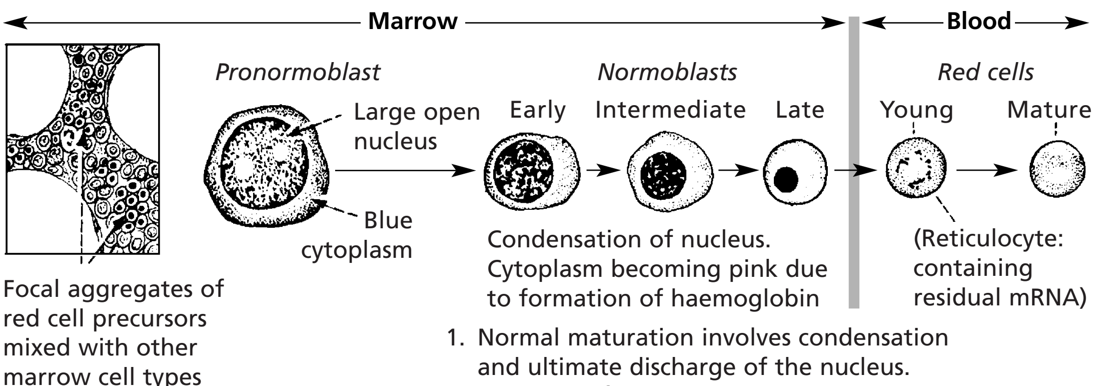
Film of aspirate allows detailed observation of **cell morphology**.



Histological preparation of trephine material allows assessment of **architecture**.

ERYTHROPOIESIS

Normal marrow erythropoiesis is said to be NORMOBLASTIC.



1. Normal maturation involves condensation and ultimate discharge of the nucleus.
2. Synthesis of haemoglobin in the cytoplasm.
3. Diminution in cell size.

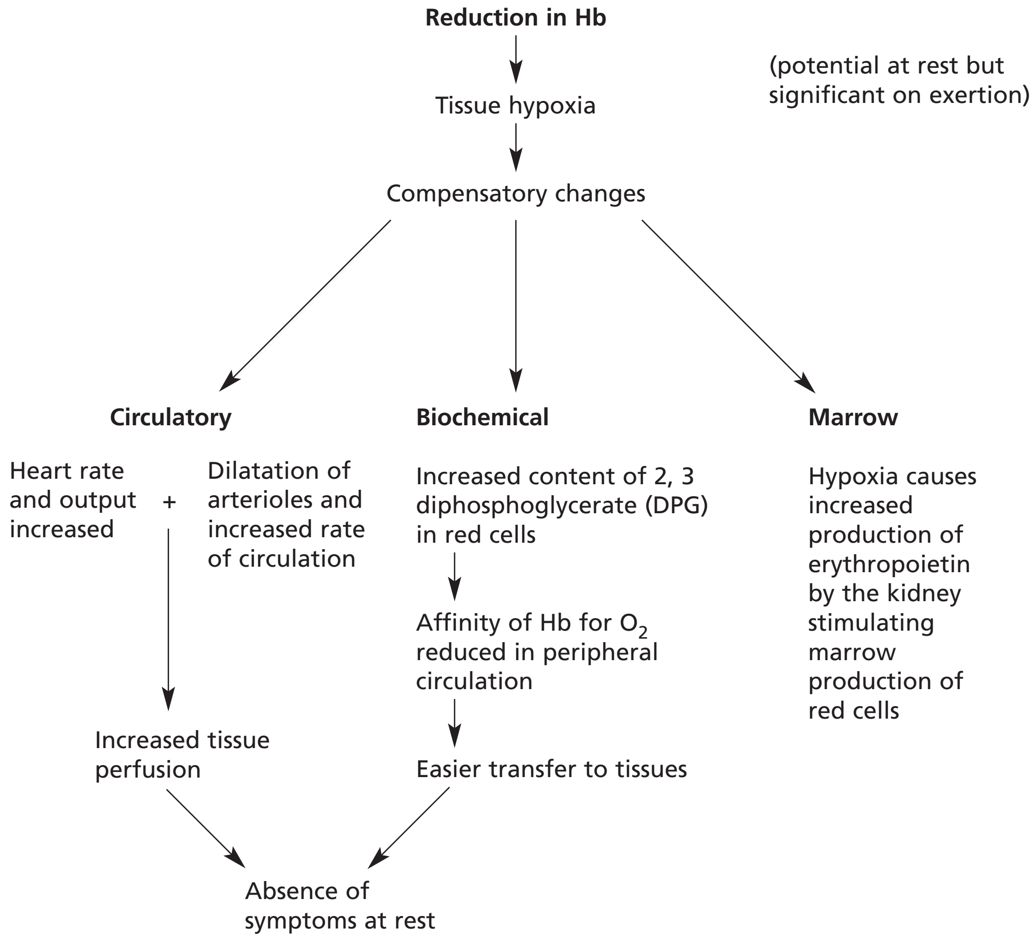
When the essential factors vit. B_{12} or folic acid are deficient, the red cell precursors show clear morphological changes – erythropoiesis is said to be MEGALOBLASTIC (p.386).

ANAEMIA

The most important function of the red cell is the transport of oxygen bound to haemoglobin. The most common and important disorder associated with disease of the red cells is ANAEMIA, which is defined as a reduction below normal of the concentration of haemoglobin in the blood.

Anaemia in men – Hb < 13 g/dl: in women – < 11.5 g/dl.

Effect of anaemia



Clinical associations

1. Diminished exercise tolerance, i.e. dyspnoea on exertion.
2. Rapid, full, bounding pulse: decreased circulation time.

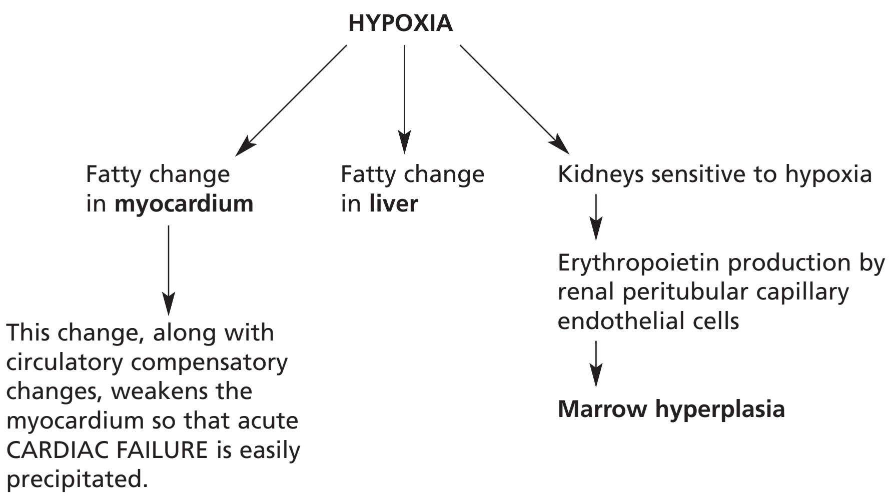
ANAEMIA

The effects of anaemia depend on its severity, rate of development and duration.

In slowly developing moderate anaemias, symptoms such as dyspnoea only appear on exertion, and even when the haemoglobin falls as low as 6–7 g/dl, clinical features may be slight.

Pathological complications of anaemia

1. Effects of degenerative arterial disease are aggravated, e.g. symptoms of ANGINA PECTORIS and lower limb CLAUDICATION are increased.
2. In severe anaemias effects are seen in organs.



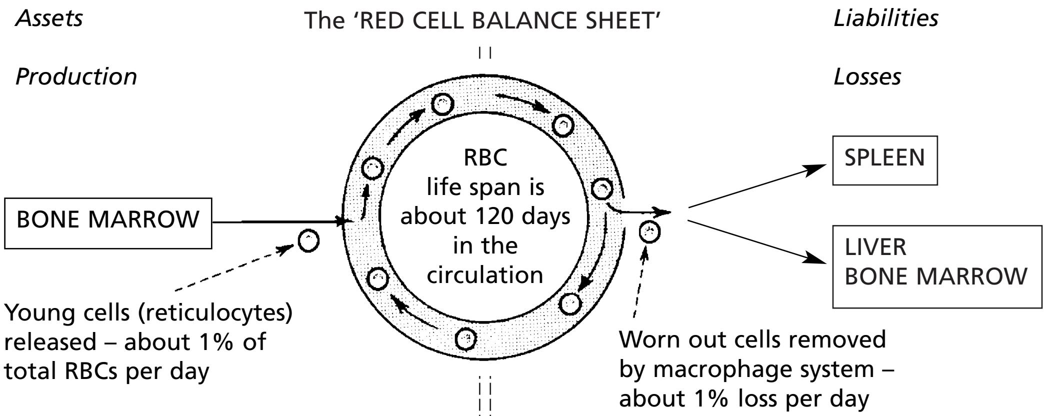
Note: Therefore blood transfusion used in the treatment of anaemia is given ***slowly*** and as ***packed cells*** to avoid fluid overload.

In very rapidly developing anaemias, the compensatory mechanisms cannot adjust adequately – the condition merges into SHOCK.

ANAEMIA

Causes of Anaemia

An understanding of the **four main mechanisms** by which anaemia develops depends on a knowledge of the life-cycle of red blood cells.



Mechanisms

(A) in the marrow		(B) in the circulation	
(i)	(ii)	(iii)	(iv)
Reduced production by marrow (hypoplasia or aplasia) or marrow replacement by tumour.	Marrow unable to produce sufficient normal red cells, usually due to deficiency of an essential factor. e.g. iron: Vit B_{12}.	Excessive loss of RBCs due to haemorrhage.	Excessive destruction of RBCs by the macrophage system particularly in the spleen (a) of normal RBCs, e.g. in hypersplenism or autoimmunity. (b) of abnormal cells, e.g. in hereditary spherocytosis.
↓	↓	↓	↓
HYPOPLASTIC ANAEMIAS	DYSHAEMOPOIETIC ANAEMIAS	POST-HAEMORRHAGIC ANAEMIA	HAEMOLYTIC ANAEMIAS

Note: Many forms of anaemia have more than one component.

e.g. 1. The abnormal cells produced in hypoplastic and dyshaemopoietic anaemias have a shortened life span so that a haemolytic element is superimposed.

2. The anaemia of chronic blood loss is almost wholly dyshaemopoietic due to the loss of iron.

ANAEMIA

HYPOPLASTIC and APLASTIC ANAEMIAS

These are rare conditions and, as the names imply, are due to marrow failure with diminished numbers or absence of haemopoietic cells. Usually all three marrow cell lines are affected, resulting in pancytopenia in the peripheral blood.

Marrow failure of this type is dealt with in detail on page 407.

Marrow failure due to extensive tumour infiltration or fibrosis also occurs.

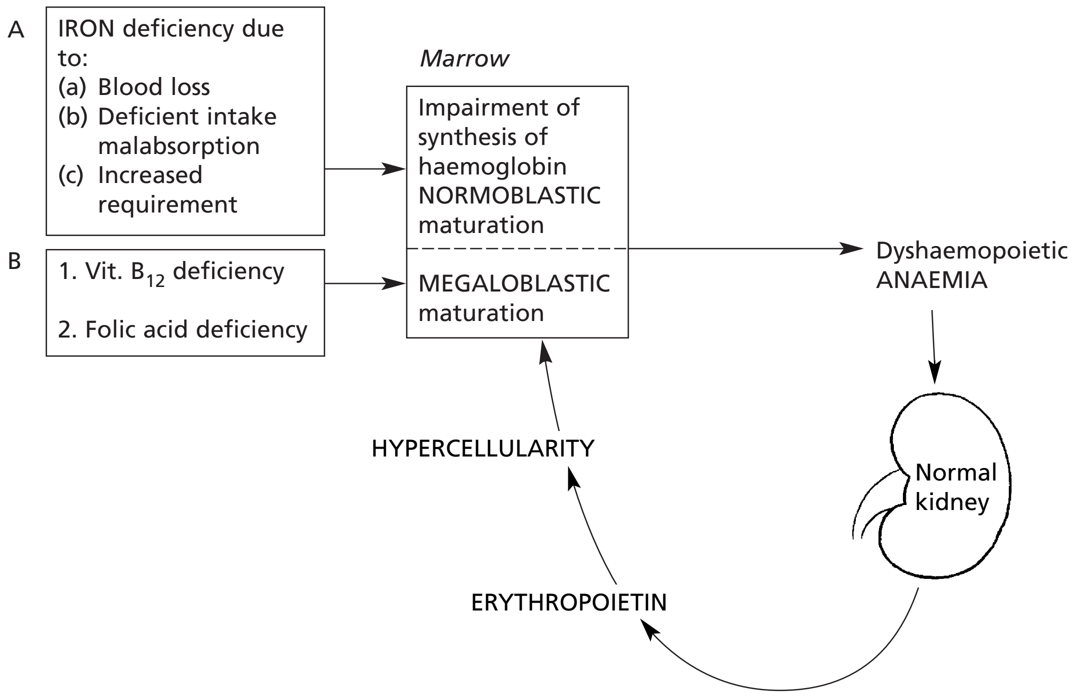
The anaemias associated with miscellaneous chronic diseases ('Secondary' anaemias) are dealt with on page 408.

DYSHAEMOPOIETIC ANAEMIAS

The usual cause of these anaemias is deficiency of an essential factor required for proper haemoglobin synthesis or erythroblast maturation and development. They are associated with a hypercellular marrow and are divided into two main groups:

(1) normoblastic and (2) megaloblastic, depending on the type of erythroblastic maturation in the marrow.

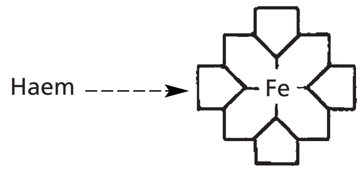
Deficiency of essential factor



IRON DEFICIENCY ANAEMIA

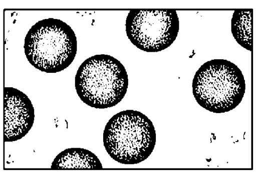
IRON DEFICIENCY ANAEMIA is the commonest anaemia on a world basis due to (a) poor nutrition, (b) intestinal parasites (esp. hookworm) causing bleeding and (c) multiple pregnancies.
In Western countries, in the adult male and post-menopausal women, iron deficiency anaemia is nearly always due to gastrointestinal blood loss from cancer, peptic ulceration, aspirin and non-steroidal ingestion, etc. Without IRON the haem component of the haemoglobin molecule cannot be synthesised.

IRON DEFICIENCY
↓
DEFECTIVE SYNTHESIS OF HAEMOGLOBIN
↓
ANAEMIA



Changes in the blood: The red cells which show:
MICROCYTOSIS (cells smaller — mean diameter < 6.7 µm)
HYPOCHROMASIA (contain less haemoglobin ∴ less well stained)
ANISOCYTOSIS – variation in size
POIKILOCYTOSIS – variation in shape

Normal



Fairly uniform red cells – size and shape (mean diameter 7 µm)

Iron deficient



Central pallor
Variation in size – anisocytosis
Variation in shape – poikilocytosis

Parameter	Low/High	Normal Range
MCV (mean cell volume)	LOW (< 80)	80–92 fl
MCH (mean cell haemoglobin)	LOW (< 27)	27–32 pg
MCHC (mean corpuscular haemoglobin concentration)	LOW (< 30)	33 g/dl
Serum IRON	LOW	10–30 mmol/l
Serum FERRITIN	LOW	15–300 mg/l
Serum IRON BINDING CAPACITY	RAISED	45–70 mmol/l
Serum IRON SATURATION $\left[\frac{\text{IRON}}{\text{Binding capacity}}\right] \times 100$	LOW	16–60%

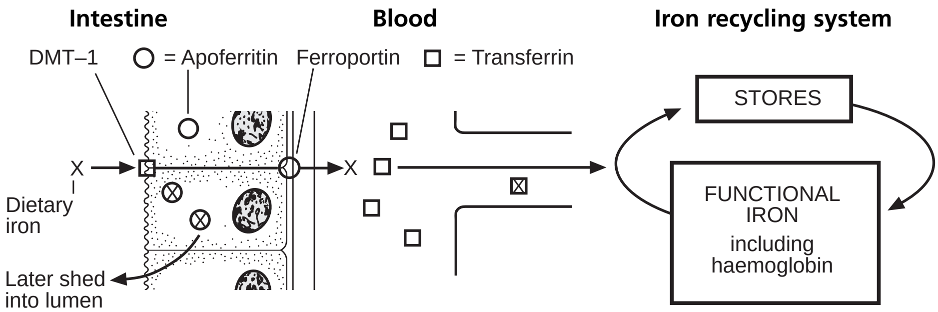
The **reticulocyte count** is NORMAL except following episodes of haemorrhage. Usually there are no changes in the leucocytes and platelets.

The **bone marrow** is hypercellular and contains small, poorly haemoglobinised normoblasts; iron stores are reduced.

IRON DEFICIENCY ANAEMIA

IRON METABOLISM

Iron is absorbed mainly in the duodenum and upper jejunum. Only small amounts are normally required to replace iron losses. Since the average diet contains more iron than is required, its absorption is controlled by the *mucosal apoferritin mechanism*.



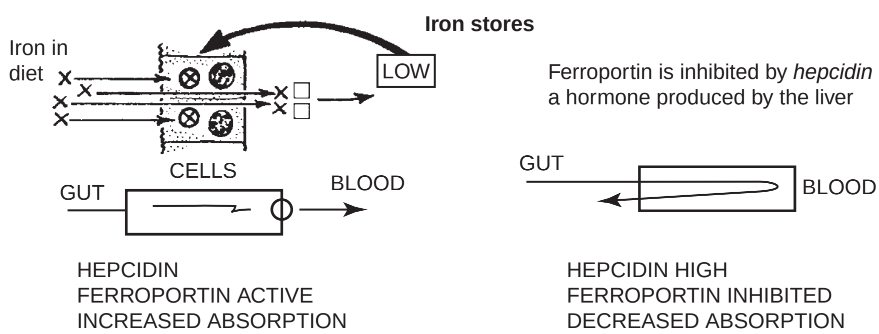
The iron (X) in the diet enters the mucosal cell through an apical uptake transporter (DMT-1) and having combined with apoferritin (O) is retained in the cell as ferritin (⊗).

Note: This bound iron is subsequently shed along with the cell into the lumen.

Iron unbound by apoferritin passes through the cell through a basolateral transporter (ferroportin) and is transported in the blood to join the iron recycling system.

Note: New haemoglobin formed in the bone marrow contains 95% iron from recycling system, 5% from diet.

The state of the iron stores controls the apoferritin (a form of intracellular transferrin) content of the intestinal mucosal cell by a feed-back mechanism.



ACUTE IRON OVERLOAD

If a large dose of medicinal iron preparations is taken (particularly by children in error) the absorption and transport mechanisms are overwhelmed and free iron radicals exert very toxic effects.

IRON DEFICIENCY ANAEMIA

The iron balance may be summarised as follows.

INPUT
(Adult male)

Average: 1 mg/day
derived from foods
(a) animal muscle
(b) vegetables.
The average diet contains 10–20 mg iron, of which about 10% is absorbed.
In the adult female, the average daily input is about 2 mg.

BODY IRON
Total 3–6 g

(a) *Functional iron*
in haemoglobin, myoglobin, enzyme systems, transferrin } 70% at least

(b) *Storage iron*
in liver, spleen, bone marrow as ferritin, haemosiderin } 30% or less

OUTPUT

Average: 1 mg/day
Skin desquamation and miscellaneous secretions

Menstruation
This extra loss of about 0.5 to 1 mg requires extra input in the female

Anaemia results when this balance is upset in:

1. *Increased output* This almost always is caused by blood loss – often small in amount and chronic (1 ml blood = 0.5 mg iron). In the female, uterine bleeding is a common cause, and in both sexes bleeding from the gastrointestinal tract is important.
2. *Decreased input*
   (a) Poor diet (including diets containing substances antagonistic to iron absorption, e.g. phytates, phosphates)
   (b) Malabsorption – due to bowel disease, e.g. coeliac disease, or post-surgical, e.g. post-gastrectomy.
3. *Increased body requirement*
   (a) During rapid growth in childhood
   (b) In pregnancy.

Usually anaemia develops slowly (except in cases of serious haemorrhage).

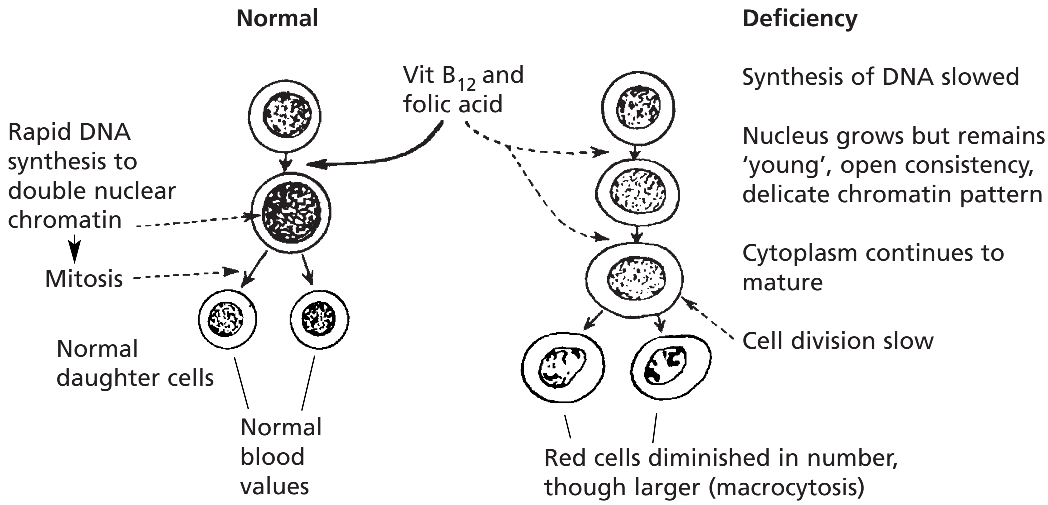
(1) Iron deficiency → (2) Mobilisation of reserves → (3) Exhaustion of reserves → (4) Deficient synthesis of haemoglobin → (5) Anaemia

Increased absorption if available in diet may postpone (4)

THE MEGALOBLASTIC ANAEMIAS

These dyshaemopoietic anaemias are almost always caused by deficiency of either vitamin B_{12} or folic acid which are intracellular co-enzymes, particularly important for the synthesis of DNA.

The effects of deficiency occur in most organs of the body but are prominent where cell turnover is rapid, e.g. in the **marrow**.



Results in organs particularly affected

1. MUCOUS MEMBRANES of alimentary tract and genitalia → Regenerative activity cannot balance surface cell losses → THINNING (atrophy) often with functional deficiencies

2. BONE MARROW blood cell precursors of all series affected → Many immature red cells are destroyed in the marrow. Red cells released into blood have a shortened life span. → Megaloblastic

   Increased growth factors cause increased cellularity. → Hypercellular

Note:

(a) Vit B_{12} (but not folic acid) has a separate function in the maintenance of the integrity of myelin. Therefore deficiency leads to neuropathies – particularly **subacute combined degeneration** (p.391).

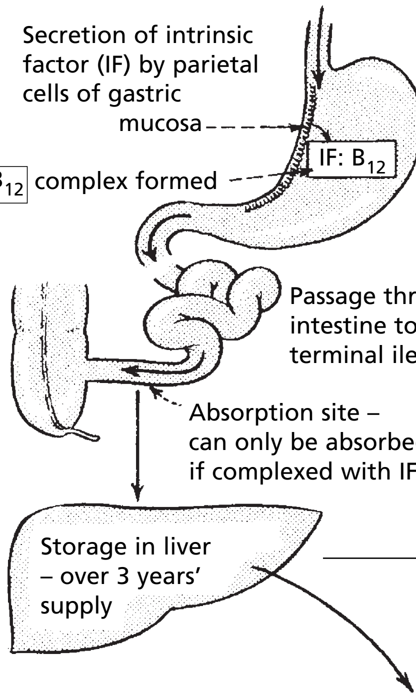
(b) The marrow and blood appearances are similar in deficiency of vit B_{12} and folic acid from any cause. The classic disease of this type is **pernicious anaemia**.

PERNICIOUS ANAEMIA (PA)

This serious and severe anaemia was first described by the English physician Addison in the mid 19th century. At that time it was invariably fatal, but now is treatable. It is due to vitamin B_{12} deficiency and is always associated with achlorhydria and gastric mucosal atrophy, due to autoimmune gastritis.

Vitamin B_{12} metabolism and causes of deficiency:

Normal	Deficiency of vitamin B_{12}: In PA	Deficiency of vitamin B_{12}: Other causes
Source: Food – vit B_{12} in animal products, e.g. meat, eggs. Daily requirement = 1 µg	Normal	Dietary deficiency, e.g. strict vegans – takes many years to develop.
Secretion of intrinsic factor (IF) by parietal cells of gastric mucosa; IF: B_{12} complex formed	Gastric atrophy No IF ∴ No IF: B_{12} complex	Surgical operations on stomach, e.g. gastrectomy.
Passage through intestine to terminal ileum	Normal	Loss during passage in intestine, e.g. utilised by tape worms or bacteria (blind loop syndrome).
Absorption site – can only be absorbed if complexed with IF	No absorption	Disease of ileum, e.g. Crohn's disease: ileal resection.
Storage in liver – over 3 years' supply		Gradual depletion of liver stores over several years



Released into blood stream bound to transcobalamin to act as important co-enzyme in several intracellular synthetic pathways but particularly of DNA.

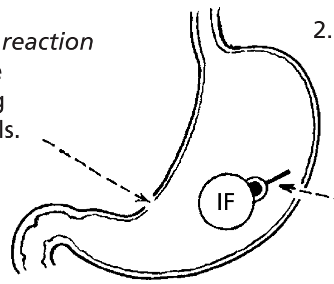
Especially important to:

1. Bone marrow .... ANAEMIA (MEGALOBLASTIC)
2. Nervous system ...... ± NERVE CHANGES
3. Epithelial coverings ... ± TONGUE MUCOSAL ATROPHY

PERNICIOUS ANAEMIA (PA)

Mechanism of production of gastritis

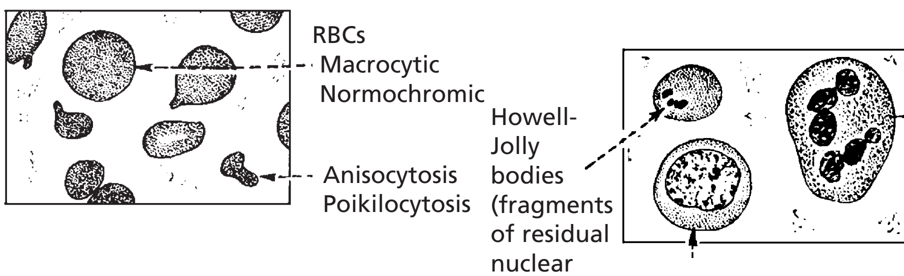
PA is an autoimmune disease. The gastric atrophy is caused by an immune reaction against parietal cell cytoplasmic constituents and specifically by antibodies to intrinsic factor (IF).



There is an increased familial incidence of PA and other organ specific autoimmune diseases, e.g. Hashimoto's thyroiditis.

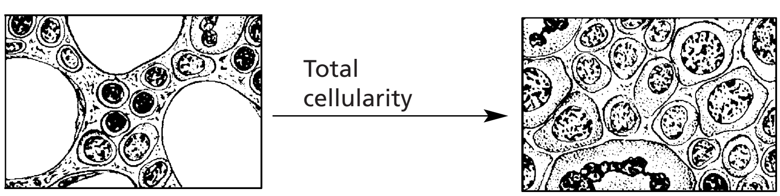
Blood changes

There is a pancytopenia, i.e. reduction in RBCs, granulocytes and platelets but the red cells are larger (macrocytosis).



Marrow changes

Hyperplasia – often complete cellularity in flat bones and extension down length of femur.



Associated changes

1. *Nervous system*

(a) Subacute combined degeneration of spinal cord.

Note: This serious degeneration may occur before clinical anaemia is present, and is aggravated by the administration of folic acid.

(b) Peripheral neuropathy – both sensory and motor loss.

2. *Epithelial surfaces*

Atrophy is common especially in the tongue and vagina – where senile atrophy is aggravated.

FOLIC ACID DEFICIENCY

FOLIC ACID (Pteroyl-glutamic acid) DEFICIENCY

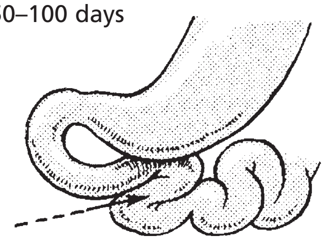
Normal metabolism

Source
Polyglutamines in green vegetables, cereals, meat, fish and eggs (not milk)

Minimum daily requirement
50 µg

Body reserves 50–100 days

Absorption
As mono-glutamate in jejunum



Utilisation
For DNA synthesis. Vit B_{12} is necessary for synthesis of the active tetrahydrofolate form (FH4)

Deficiency

Dietary
Low intake of vegetables.
Anorexia, alcoholism, poverty (elderly), infants (late weaning)

Increased requirements
Pregnancy (fetal growth)
Infancy and childhood (rapid growth)
Haemolysis
Malignancy

Malabsorption
Coeliac disease
Surgical by-pass

Utilisation block
Drugs e.g. methotrexate in cancer chemotherapy also anti-convulsants e.g. phenytoin.

Note:
1. Since the marrow and blood changes in folic acid and vitamin B_{12} deficiency are similar, the differential diagnosis has to be obtained by other laboratory tests – particularly the measurement of vit B_{12} in the serum and of folic acid in RBCs. Special tests of absorption of vit B_{12} (e.g. Schilling test) are available.
2. Since vit B_{12} and folic acid deficiency are often associated with malabsorption, other deficiencies (e.g. iron) may co-exist.
3. All megaloblastic anaemias are macrocytic, but *not all* macrocytic anaemias are megaloblastic.
4. There is a strong association between folic acid deficiency in PREGNANCY and congenital neural tube defects.

THE HAEMOLYTIC ANAEMIAS

HAEMOLYTIC ANAEMIAS

In all haemolytic anaemias, there is a reduction in the life span of the red cells; due to an increased rate of red cell destruction – haemolysis.

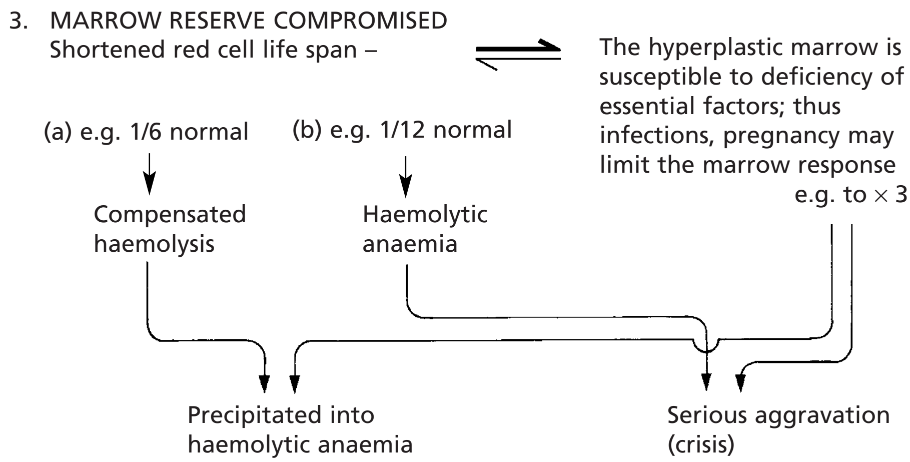
Red cells may be destroyed
(a) in the spleen, liver – extravascular haemolysis.
(b) in the blood stream – intravascular haemolysis, with release of haemoglobin into plasma.

1. COMPENSATED ERYTHROPOIESIS
   Shortened red cell life span – e.g. 1/6 normal (20 days) $\rightleftharpoons$ Marrow production increased $\times$ 6

   Balance maintained ------ $\therefore \rightarrow$ No anaemia

2. ANAEMIA
   Shortened red cell life span – e.g. 1/12 normal (10 days) $\rightleftharpoons$ Marrow production increased maximally $\times$ 8 to 10 normal

   Balance not maintained ------ $\therefore \rightarrow$ Anaemia

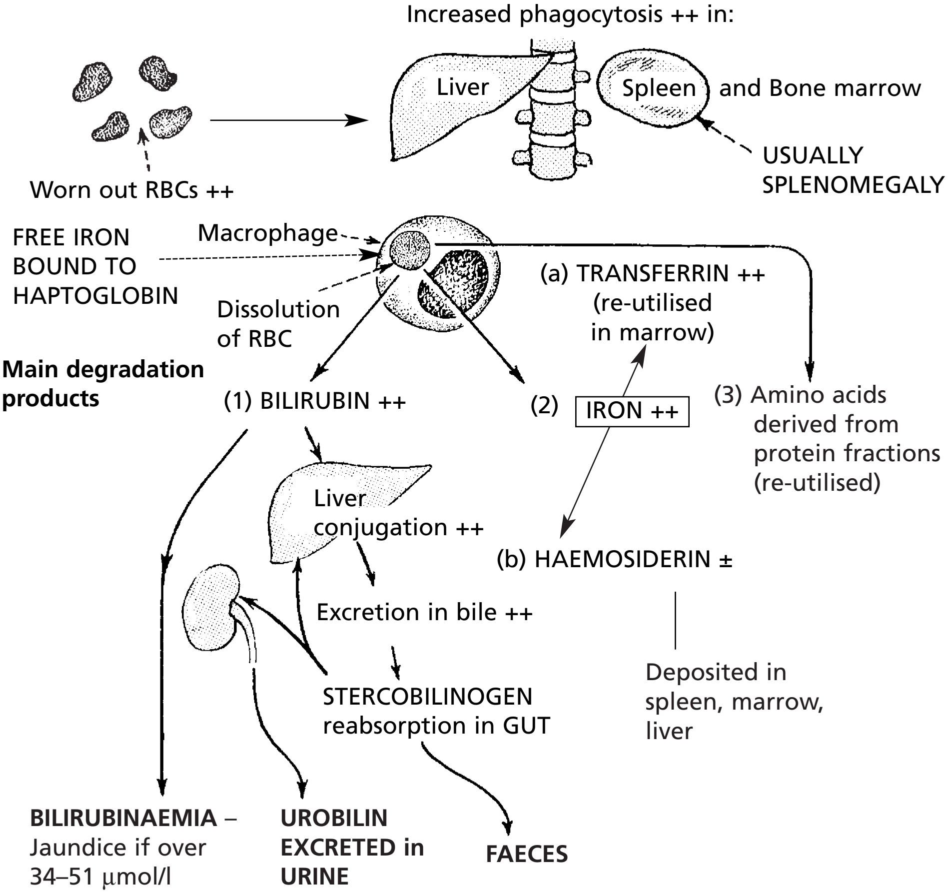


Functional reserve can compensate for a certain level of haemolysis but this fails when the degree of red cell loss is extreme or when the marrow function is compromised by other factors.

THE HAEMOLYTIC ANAEMIAS

Effects of the increased degradation of haemoglobin

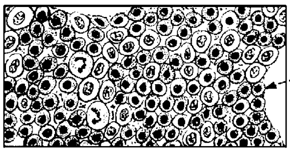
In most haemolytic conditions, the red cells are removed and the haemoglobin degraded in the usual way, i.e. by phagocytosis by the macrophage system.



Note: 1. The bilirubin is unconjugated and is attached to protein so that renal excretion does not occur – **acholuric jaundice.**
2. Unconjugated bilirubin is toxic to the central nervous system of neonates; **kernicterus** (see p.394) is a serious complication of haemolytic disease of the newborn.
3. If haptoglobin reserves are saturated, Hb remains free in plasma causing kidney damage and haemoglobinuria.

REACTIVE BONE MARROW CHANGES

There is a marked hyperplasia ——— Extension of RED MARROW into long bones



Marrow packed with well haemoglobinised normoblasts

± Haemosiderin depending on rate of iron utilisation

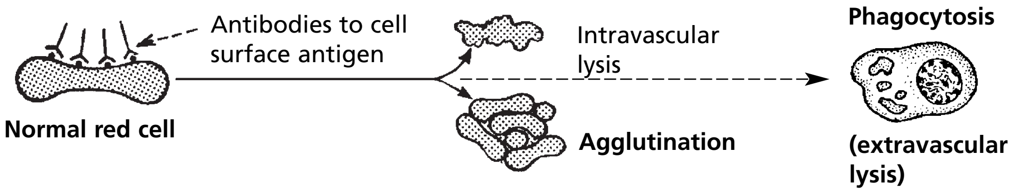
Many young red cells are released into the blood. The reticulocyte count may be 20–30%.

EXTRINSIC HAEMOLYTIC ANAEMIAS

The causes of shortened red cell survival are divided into 2 main groups.

1. EXTRINSIC (factors outside the red cells) and 2. INTRINSIC (defects of red cells).
Extrinsic haemolytic anaemias fall into 4 groups due to:
(a) **ANTIBODIES** (either auto-immune or iso-antibodies, (b) **Infections**,
(c) **Chemical damage** to the red cell and (d) **Physical damage** to the cell.

(1a) AUTOIMMUNE HAEMOLYTIC ANAEMIA



Auto-immune haemolytic anaemias are classified according to the temperature at which the reaction occurs and the presence of an underlying cause.

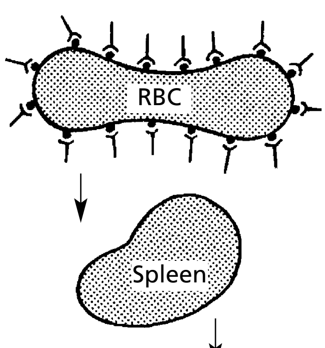
WARM (37°C – usually IgG)

Primary – so-called idiopathic haemolytic anaemia: usually in adults.

Secondary – associated with
- (i) **lymphomas** e.g. chronic lymphocytic leukaemia, Hodgkin's disease.
- (ii) **other cancers.**
- (iii) **connective tissue diseases** e.g. systemic lupus erythematosus, rheumatoid arthritis.
- (iv) **drugs** e.g. methyl dopa.

Mechanism:
Coating of RBC with IgG antibodies often against Rhesus 'e' antigens.

Destruction in spleen which is often enlarged.

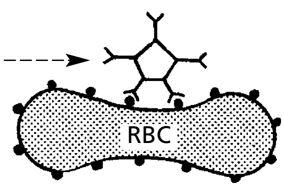


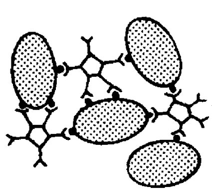
Chronic haemolytic anaemia + crises

COLD (< 30°C – usually IgM)

Idiopathic cold agglutination disease
- (i) lymphomas.
- (ii) *Mycoplasma pneumoniae*.
- (iii) viral infections e.g. measles.

Mechanism
IgM antibody → combines with RBC





Agglutination → Blockage of peripheral vessels → **Painful hands and feet**

Complement activation → Intravascular lysis → **Paroxysmal cold haemoglobinuria**

INCOMPATIBLE BLOOD TRANSFUSION/ HAEMOLYTIC DISEASE OF THE NEWBORN

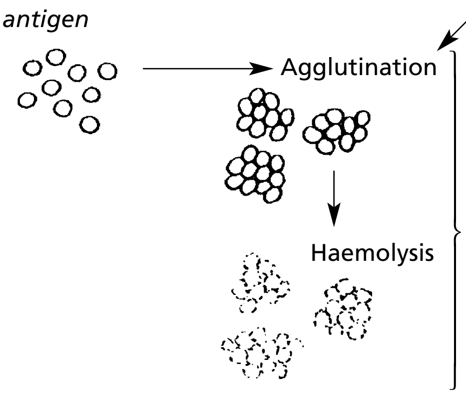
(1b) **DESTRUCTION of RBCs is due to ISO-ANTIBODIES**

In these, the antibodies act against antigens which are derived from another individual of the same species.

Incompatible ABO blood transfusion is a classic example.

e.g. **Donor Blood**
Group A
i.e. cells contain
A antigen

Recipient
Group O (cells contain neither A nor B antigen)
Plasma contains *Anti-A* (iso-antibody) (and Anti-B)



Clinical and pathological effects

Rigor: loin pain
Haemoglobinuria
Jaundice (after 12 hours)
SHOCK → maybe DEATH

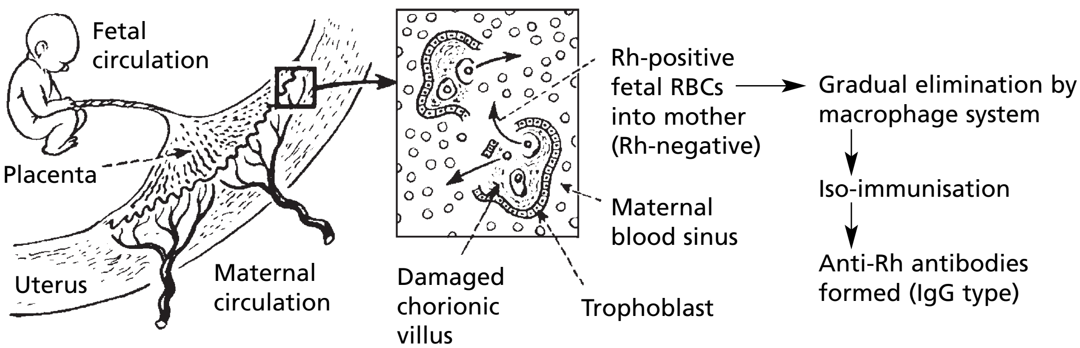
Perhaps later:
Haemostatic failure ⟶ maybe DEATH
Renal failure

(1c) **HAEMOLYTIC DISEASE OF THE NEWBORN (HDN).** This occurs in Rhesus positive fetuses conceived by Rh-negative mothers. The usual mechanism is as follows:

First pregnancy: Rh-positive fetus in Rh-negative mother – no antibodies present;
∴ *Healthy Baby*

But during this pregnancy, iso-immunisation of the mother may occur.

Towards term and particularly during labour the placental barrier is breached and fetal RBCs enter the maternal circulation.



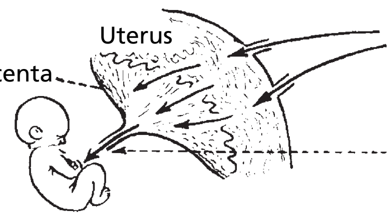
HAEMOLYTIC DISEASE OF THE NEWBORN

The basic mechanism is influenced by three important factors:

(a) The maternal immune response tends to be proportional to the number of fetal cells entering the circulation.
(b) The maternal immune response is boosted in successive Rh incompatible pregnancies – the highest maternal antibody titres are found in the latest of multiple pregnancies.
(c) Fetal/maternal ABO compatibility influences the Rh immune response.

e.g. ABO compatible		*ABO incompatible*	
Fetus	*Mother*	*Fetus*	*Mother*
Group O Rh+	Group O Rh−	Group A Rh+	Group O Rh−
Gradual elimination of fetal cells		Rapid destruction of fetal cells	
∴ *Maximum* immune response		∴ *Minimum* immune response	

Subsequent pregnancies: All Rh-positive fetuses conceived by a mother who has acquired anti-Rh antibodies either during previous pregnancies or by blood transfusion (in this case the first fetus also) are at risk.



Maternal anti-Rh antibodies IgG type
↓
Pass placental barrier
↓
Enter fetal circulation and **destroy fetal red cells** (agglutination and haemolysis)

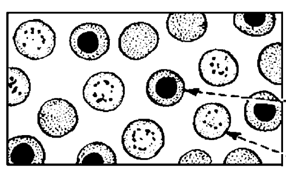
The effects are graded into three categories of severity:

(1) **Congenital haemolytic anaemia**
Usually mild anaemia and jaundice
↓
Usually self limited

(2) **Icterus gravis neonatorum**
Rapidly developing severe **anaemia** and **jaundice**
→ ± Brain damage due to kernicterus
→ Severe anoxia may cause death
→ **Hepatosplenomegaly** – due to extramedullary **haemopoiesis**

(3) **Hydrops fetalis**
Stillbirth associated with severe anoxia in utero with cardiac failure and oedema
↓
Hepatosplenomegaly – due to extramedullary **haemopoiesis**

Film of cord blood



Very numerous nucleated red cells

Reticulocytes +++ (e.g. 30%)

Modern prophylaxis
Injection of anti-Rh antibody minimises immune response.

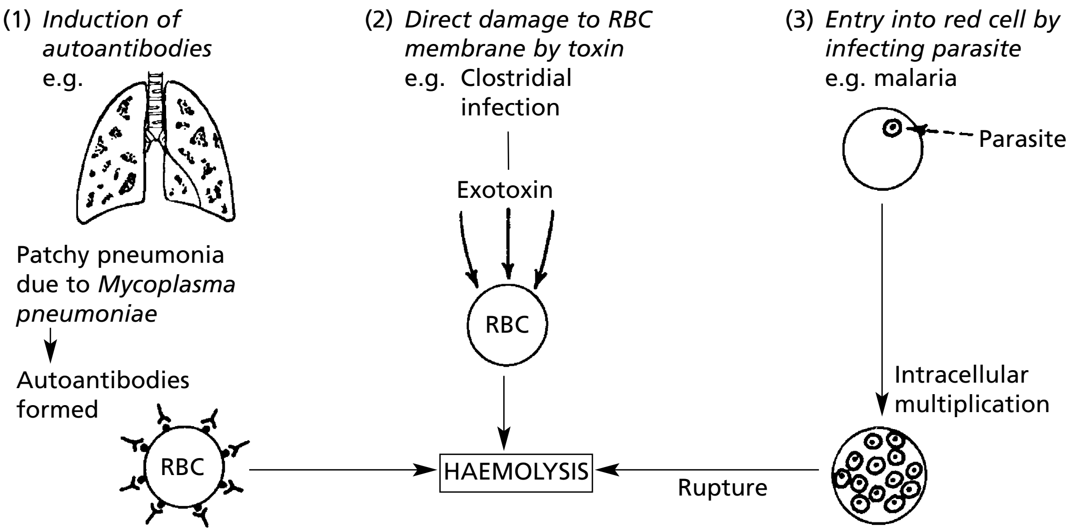
Anti-Rh (anti-D) usually obtained from male volunteers → Rh negative mothers immediately following delivery – Rh positive fetal cells in circulation → Agglutination and rapid elimination

Minimal or no immune response

EXTRINSIC HAEMOLYTIC ANAEMIAS

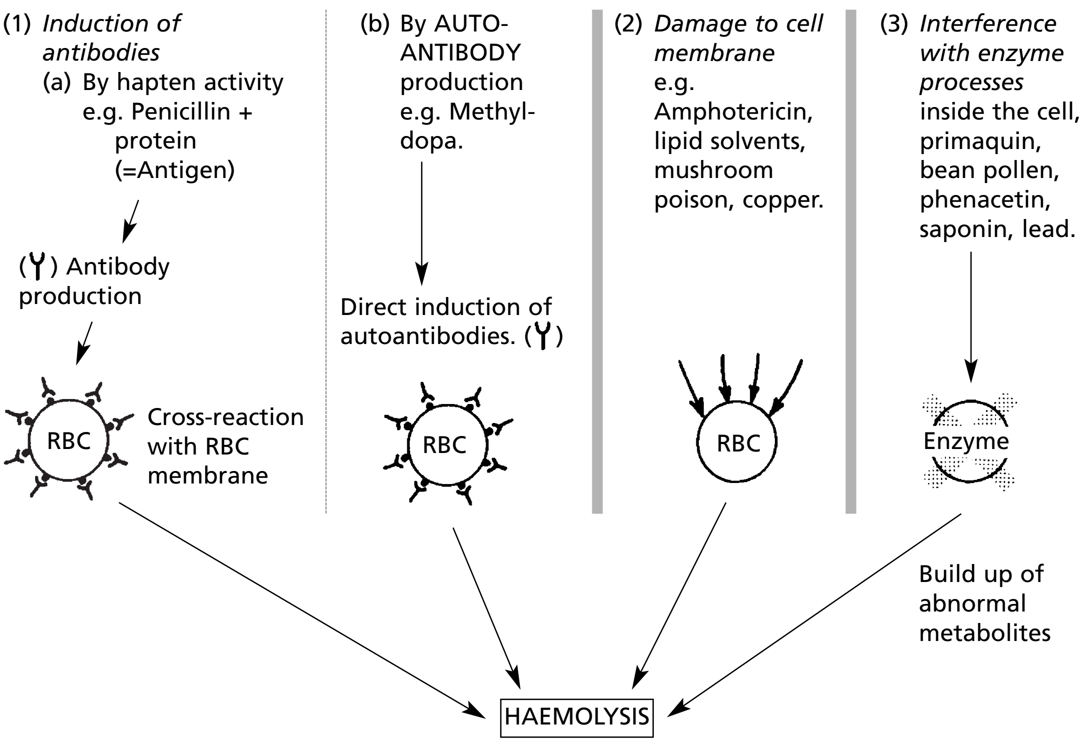
2. **INFECTIONS**

There are three mechanisms by which infections cause haemolysis:



3. **DRUGS AND CHEMICALS**

The three main mechanisms by which drugs and chemicals cause haemolysis are:



EXTRINSIC HAEMOLYTIC ANAEMIAS

4. **MECHANICAL TRAUMA**

The results of damage to red cells within the circulation are:

(1) Intravascular haemolysis → Haemoglobinuria

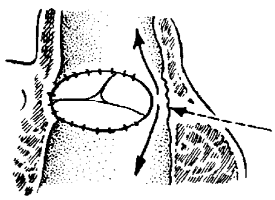
(2) Formation of red cell fragments (schistocytes)



The main circumstances in which red cells are damaged are:

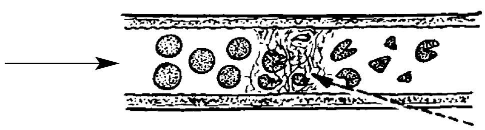
(a) In the **heart and great vessels**

When the blood flow is subjected to undue turbulence or jet effect. An important example is prosthetic valves in the left side of the heart.



(b) In the **microcirculation**

(i) When the blood flow in arterioles is impeded by strands of fibrin.



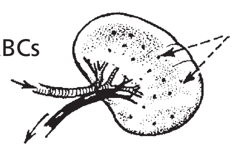
This condition is called MICROANGIOPATHIC HAEMOLYTIC ANAEMIA and occurs in many disease states involving small blood vessels e.g. malignant hypertension and/or intravascular coagulation.

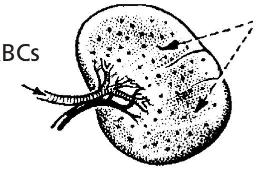
(ii) When blood vessels are subjected to direct trauma. This is seen classically in military recruits marching long distances in hard soled boots, when the blood vessels of the soles of the feet are squeezed with every step – **march haemoglobinuria.**
The haemolysis is usually not severe enough to be of clinical significance, but haemoglobinuria may cause alarm.

Other causes of haemolysis include:

Hypersplenism

In enlargement of the spleen from any cause, the sequestration of red cells is increased so that haemolytic anaemia may result.

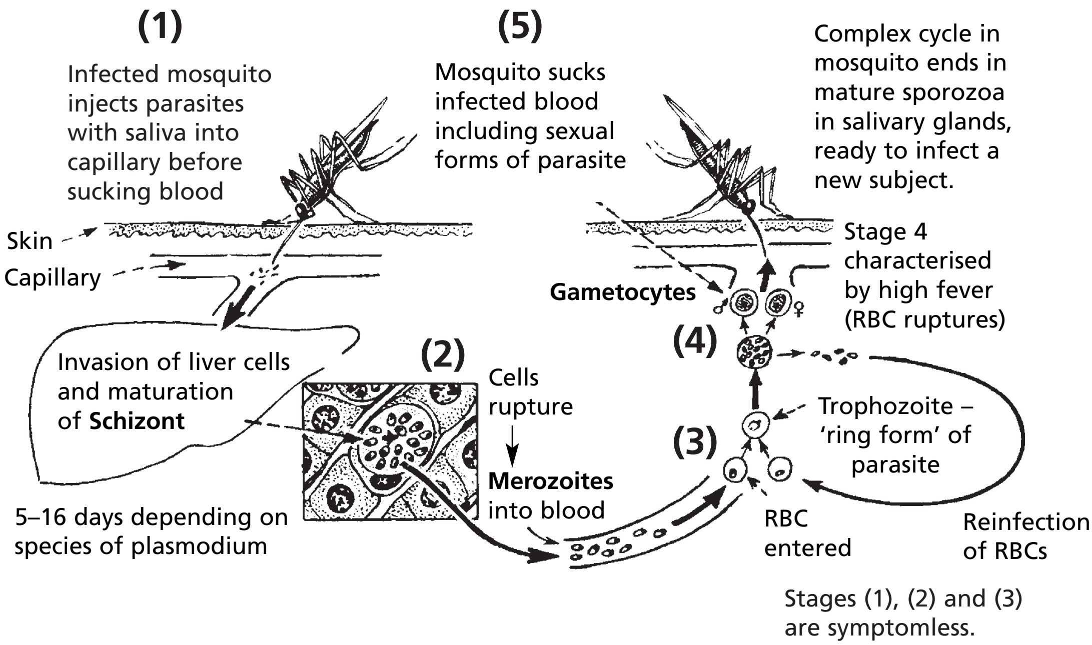




EXTRINSIC HAEMOLYTIC ANAEMIAS – MALARIA

Malaria is an endemic disease in many parts of Africa, Asia, Central and South America. Many millions of cases occur each year and the mortality is at least 1%. The disease is particularly severe in non-immune subjects from temperate climates; in endemic areas where the 'herd' immunity is high, a low grade chronic illness is common.

Female anopheline mosquitos act as intermediate hosts in the life cycle of the parasite, a protozoon (genus *Plasmodium*).



In some species, schizonts lie dormant in the liver; relapse may occur after long remissions.

Pathological changes

1. *Parasitism and destruction of red cells* → ANAEMIA (haemolytic); → Liberation of pigment and red cell debris → very marked macrophage activity → SPLENOMEGALY

In a few severe cases, massive haemolysis leads to haemoglobinuria with kidney damage – **blackwater fever.**

Cerebral malaria is due to capillary blockage by parasitised RBCs.

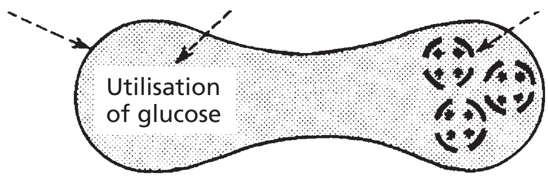
2. *Immune responses:* humoral antibodies, cellular antibodies + Macrophage activity → SPLENOMEGALY

3. *Associations:*
   (a) Recurrent attacks of malaria potentiate EB virus infection progressing to B-cell lymphoma
   (b) The sickle cell gene protects against falciparum malaria

INTRINSIC HAEMOLYTIC ANAEMIAS

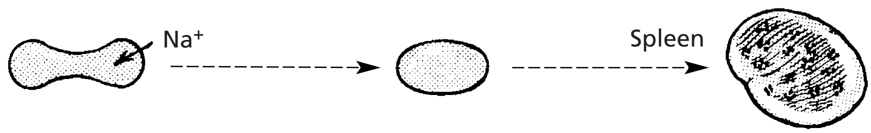
INTRINSIC DEFECTS – Usually hereditary.

In (i) cell membrane (ii) enzymes (iii) molecular structure of haemoglobin (haemoglobinopathies).



1. **Cell membrane defects**

(a) ***Hereditary spherocytosis:*** the majority of cases are familial (autosomal dominant).



The primary defect is in the proteins which support the plasma membrane – SPECTRIN and ANKYRIN.

The cells assume a spherical shape due to instability of the plasma membrane.

Premature sequestration and destruction in splenic pulp. Splenomegaly is common.

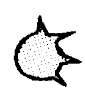
Note: Splenectomy is usually 'curative' but the red cell defect remains.

The severity of the haemolysis is variable; many cases are compensated and not anaemic, but crises are common, e.g. if folate deficiency supervenes. Intercurrent infections may precipitate increased red cell destruction with jaundice or temporary bone marrow hypoplasia, e.g. parvovirus infection, with severe anaemia.

The laboratory diagnosis depends on:
(1) typical blood film with spherocytes,
(2) high reticulocyte count and
(3) increased osmotic fragility of RBCs.

(b) ***Hereditary elliptocytosis*** is similar to spherocytosis in many respects, but it is usually not severe enough to cause anaemia or jaundice. Haemolysis is usually mild.

(c) ***Hereditary abetalipoproteinaemia***: a rare disease in which the red cell membranes are abnormal and the cells become spiky (acanthocytes).



(d) ***Paroxysmal nocturnal haemoglobinuria*** – a rare, acquired condition in which anchorage of proteins to the red cell membrane is abnormal. The cells are particularly susceptible to the action of complement (usually activated by the alternative pathway) at low pH. Intravascular haemolysis results.

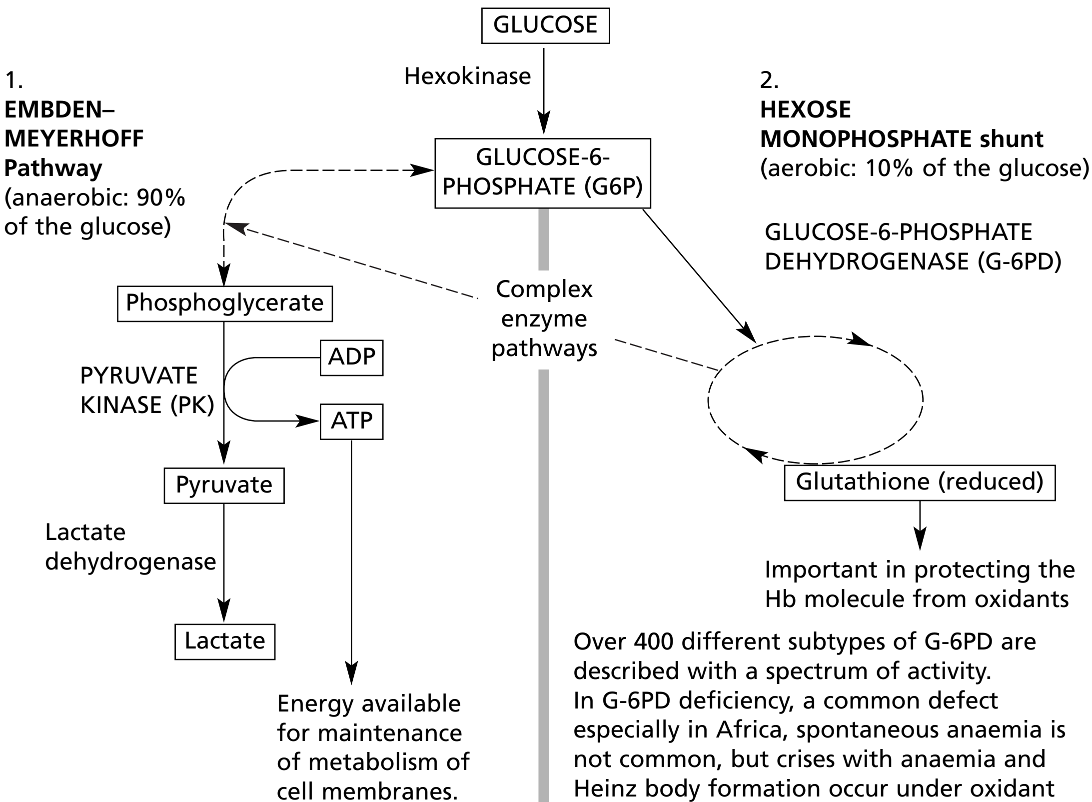
INTRINSIC HAEMOLYTIC ANAEMIAS

INTRINSIC DEFECTS of the RED CELLS (*continued*)

2. **Enzyme defects**

Usually hereditary. Glucose is the source of energy with which the red cell metabolism is maintained. Glycolysis is effected by two classic enzyme pathways.

The following simplified diagram outlines the pathways and indicates only the main enzymes and substrates.



In pyruvate kinase (PK) deficiency – a rare defect – usually mild anaemia

Over 400 different subtypes of G-6PD are described with a spectrum of activity.
In G-6PD deficiency, a common defect especially in Africa, spontaneous anaemia is not common, but crises with anaemia and Heinz body formation occur under oxidant stress, e.g. chemicals and drugs; favism (bean products). The presence of the defect may seriously aggravate haemolysis due to other causes, e.g. haemolytic disease of the newborn.

G-6PD deficiency shows X-linked inheritance so that in the male the defect is fully expressed, while in the female heterozygote there are two populations of red cells in the blood (1) normal cells and (2) defective cells.

In both these defects and in the rare defects of other enzymes in the pathways which have been described the expression of the abnormal gene is very variable from case to case.

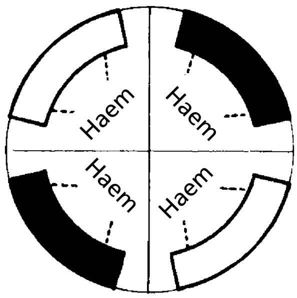
DISORDERS OF HAEMOGLOBIN SYNTHESIS

3. **Haemoglobinopathies**

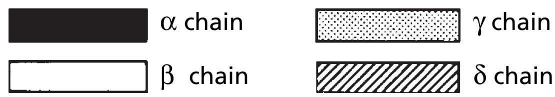
Varieties of normal haemoglobin are illustrated:

Normal haemoglobin molecule

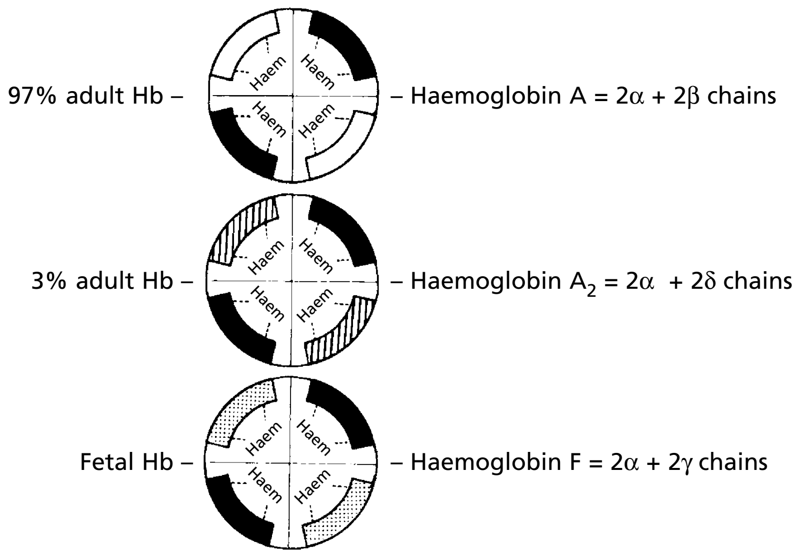
4 subunits each consisting of a haem core with a polypeptide chain attached. The haem core is constant while the polypeptide chains occur in pairs. 4 different polypeptide chains occur normally.



Mol. wt. = 68 000



There are 3 types of normal haemoglobin.



Fetal haemoglobin is replaced by adult haemoglobin during the first year ('haemoglobin switching'). Note that the α chain occurs in all normal haemoglobins.

Two copies of the α chain genes (αα/αα) are present on chromosome 16; β, γ and δ genes are found in a complex on chromosome 11. A number of globin-like genes are also present but are omitted for simplicity.

In the **thalassaemias** and **haemoglobinopathies** there are abnormalities in the production and structure of haemoglobin chains due to mutation of these genes.

THE THALASSAEMIAS

These are inherited disorders in which synthesis of globin chains is diminished or absent. They are common in the Mediterranean, Middle East and India.

α-thalassaemia – reduction of α chain synthesis.
β-thalassaemia – reduction of β chain synthesis.

Diminished production of α or β chains
Imbalance of α and β chains

↙ ↘

Reduced Hb synthesis
'Ineffective erythropoiesis'
↓
Reduced RBC production

Abnormal aggregation of globin chains
↓
Abnormal RBCs
↓
Haemolysis

↘ ↙

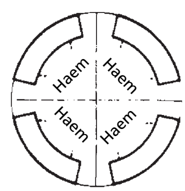
ANAEMIA
(hypochromic microcytic)

The severity of the disease depends on (i) the degree of globin chain abnormality and (ii) whether the patient is homozygous or heterozygous for the defect.

There are normally 4 α genes (αα/αα).

In the **α-thalassaemias** the genetic defects are illustrated as follows:

1. **Hb-Barts hydrops syndrome** (– – / – –)
   All 4 genes for the α chain are absent. Fetal Hb cannot be formed and the fetus dies in utero.
2. **Hb-H disease** (– α / – –): only one α gene is present.
   This leads to an excess of β chains which form tetramers called Hb-H.
   There is a moderate microcytic hypochromic anaemia with splenomegaly.



3. **α-thalassaemia** traits (– α / – α): even if two α genes are absent, the remaining two are active and the symptoms and anaemia are usually mild.

β-thalassaemia

β-thalassaemia major – two defective β genes.
The excess of α genes leads to severe anaemia with haemolysis. The marrow becomes hyperplastic and there is atrophy of bones. The main form of haemoglobin is HbF – which persists into adult life.

β-thalassaemia minor – one defective β gene.
The anaemia is mild. The red cells are microcytic and hypochromic and a mistaken diagnosis of iron deficiency anaemia can be made. These subjects act as carriers for β-thalassaemia major.

SICKLE CELL DISEASE

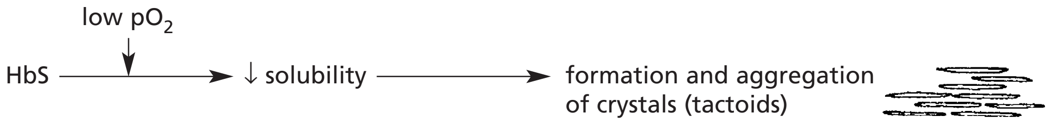
This disorder is very common in Central Africa but also occurs in the Mediterranean, Middle East and India. It affects the black population of USA and the Caribbean.

It is due to a mutation in the β chain of haemoglobin (the amino-acid glutamic acid is substituted by valine) and is inherited as an autosomal recessive trait.

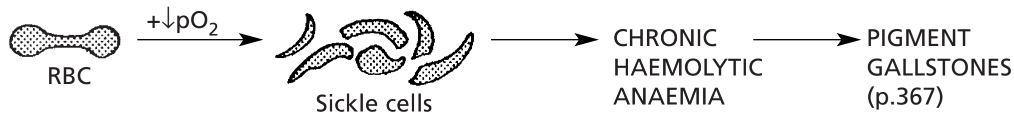
The effects are *mild* in heterozygotes (Hb AS) = **sickle cell trait**; they are severe in homozygotes (Hb SS) = **sickle cell anaemia**.

The effects are summarised as follows:

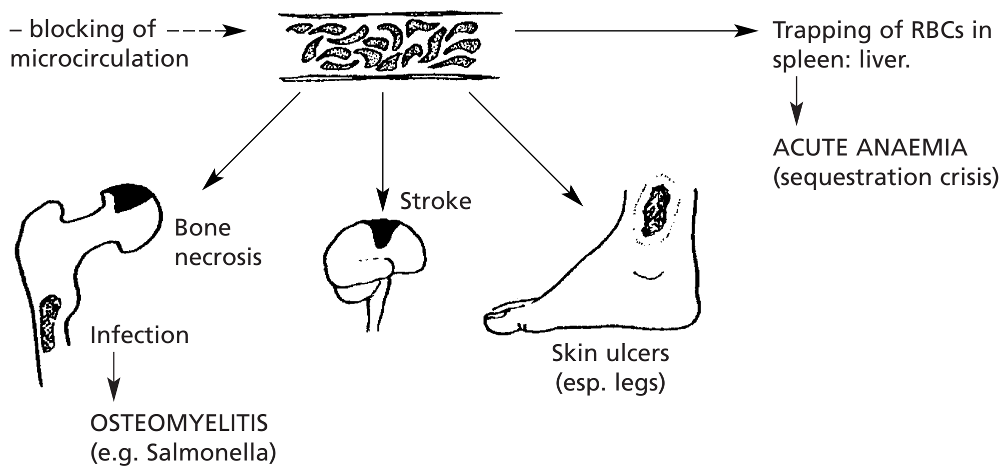
1. **At molecular level** HbS becomes less soluble in low levels of oxygen tension.



2. **In the red cell** this causes distortion (sickling).



3. **In tissues**



Acute sickle cell crises are often provoked by:

(1) infection, (2) cold, (3) low pO_2 e.g. flying in unpressurised aircraft.

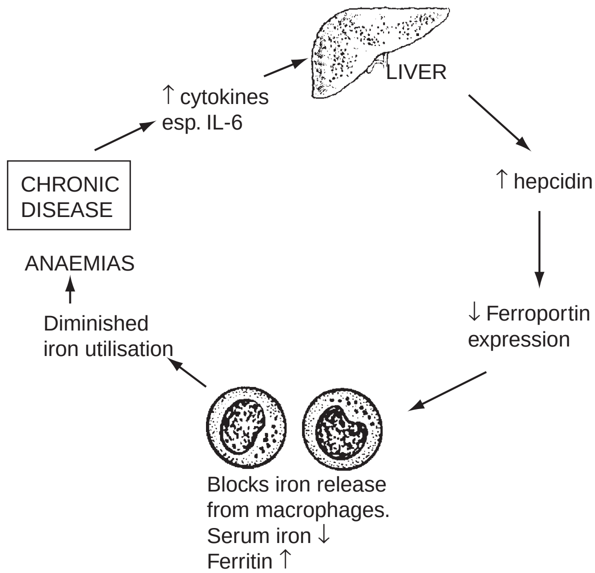
In addition, infection, especially by **parvoviruses in childhood**, may provoke an **aplastic anaemia** crisis.

Note: HbS confers resistance to malaria: in terms of evolution this confers a survival benefit to those carrying the HbS gene.

ANAEMIA OF CHRONIC DISORDERS

This term describes the anaemias seen commonly in patients with chronic diseases
e.g. (ia) Chronic inflammation e.g. rheumatoid arthritis, SLE
(ib) Chronic infection e.g. T.B.
(ii) Malignancy.

The anaemia is usually mild (Hb > 9 g/dl).



In addition, malignant tumour growth may cause anaemia by 2 more specific mechanisms.

(a) Chronic bleeding from the surface of an ulcerated tumour – especially from the alimentary tract ⟶ iron deficiency.

(b) Replacement of the bone marrow by malignant tumour.

Normocytic Normochromic Anaemias are also found in other systemic diseases.

e.g. (i) **Renal disease**
- ↓ erythropoietin ⟶ ↓ RBC production
- ↓ RBC survival – mechanism uncertain, varies with degree of **uraemia**.

(ii) **Liver failure** – additional factors are:

Liver
- Bleeding varices,
- Deficiency of coagulation factors,
- Hypersplenism,
- Alcoholic – other nutritional deficiencies.

(iii) **Endocrine disease** e.g.

hypopituitarism, hypothyroidism
- ↓ metabolism
- ↓ erythropoietin production.

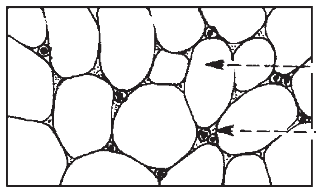
APLASTIC ANAEMIA

In this rare disorder there is:

A reduction in bone marrow stem cells → Failure of production of mature cells → Pancytopenia (of varying severity)

↓

Bone marrow is hypoplastic →

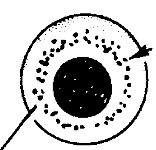


There are a number of different types
(a) **Idiopathic** – in 2/3 of cases no cause is found.
(b) **Drug induced** – this may be:
(i) Predictable e.g. Cytotoxic chemotherapy.
(ii) Idiosyncratic e.g. Chloramphenicol (1 in 25 000–60 000 affected).
Phenylbutazone.
(c) **Virus induced** e.g. Hepatitis, Epstein–Barr Virus.
(d) **Autoimmune.**
(e) **Inherited** e.g. Fanconi's anaemia – Autosomal recessive.

Treatment This consists of:
(a) Supportive therapy e.g. blood transfusion.
(b) Attempts to restore haemopoiesis e.g. bone marrow transplantation,
– anabolic steroids,
– immunosuppressive therapy,
– withdrawal of causative drugs.

The sideroblastic anaemias
In these rare anaemias, failure of synthesis of the haem component of the haemoglobin molecule is indicated by the presence of a ring of iron granules around the normoblast nucleus.

Ringed sideroblast



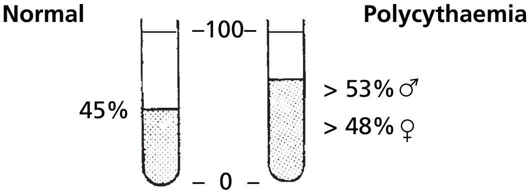
The condition arises secondarily in many of the chronic disease states mentioned on the previous page, or as a result of drug treatment or chemical poisoning (e.g. lead). Some cases are 'primary' – representing a form of myelodysplasia.

The anaemia is usually *dimorphic*; i.e. showing hypochromic and macrocytic features combined.

POLYCYTHAEMIA

POLYCYTHAEMIA

Polycythaemia (erythrocytosis) is defined by a haemoglobin level above the normal range: in true polycythaemia the red cell mass is increased and the haematocrit is always elevated.



Note: **Relative Polycythaemia** is the result of fluid loss with a decrease in plasma volume and a normal red cell mass.

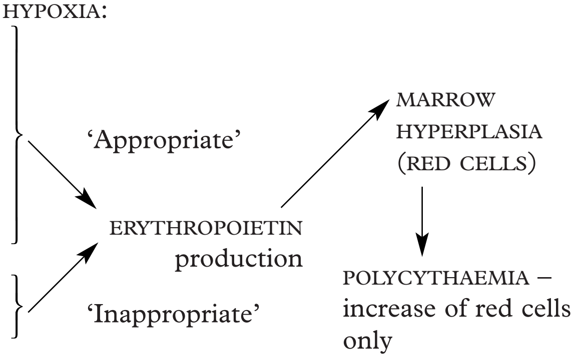
Aetiology

There are two types:

SECONDARY POLYCYTHAEMIA

The red cell increase is the result of increased stimulation of marrow by erythropoietin. Two main groups of conditions are associated with this:

1. (Commonly) Conditions causing tissue HYPOXIA:
   (a) Living at high altitudes
   (b) Chronic cardiac disease especially R → L shunts
   (c) Chronic respiratory disease
   (d) Presence of abnormal haemoglobin causing defective release of O_2 to tissues – usually hereditary.
2. (Rarely) Renal tumours and ischaemia; occasionally tumours of other organs.



PRIMARY POLYCYTHAEMIA (*Polycythaemia Rubra Vera*)

This is a myeloproliferative disorder with increased red cell production. It may be associated with an increase in other marrow elements. Splenomegaly is usually present. A minority of patients develop acute leukaemia.

Effects of polycythaemia

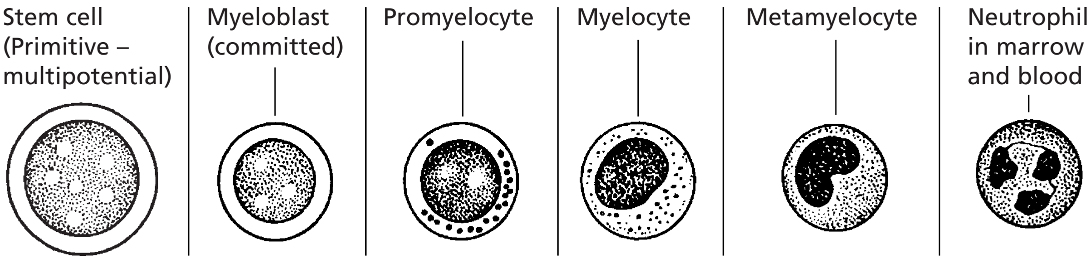
(a) There is usually a distinctly florid complexion.
(b) Increased blood viscosity causes arterial and venous thrombosis.
(c) Increased marrow activity → increased uric acid metabolism → tendency to gout.

NEUTROPHIL GRANULOCYTES

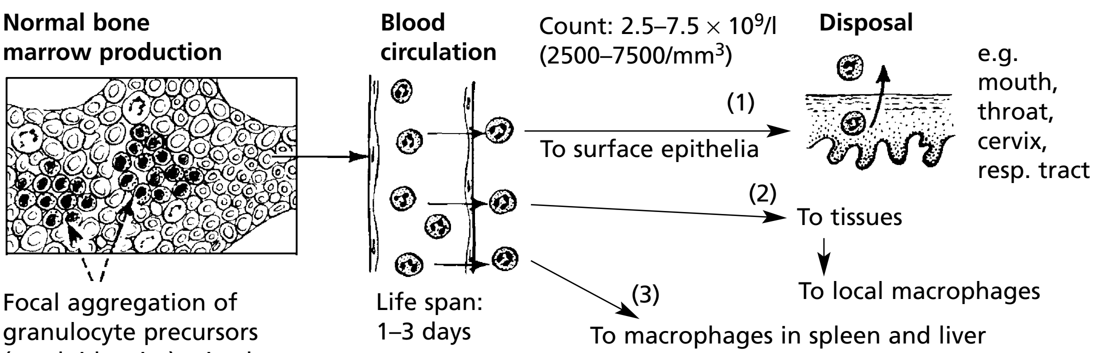
NEUTROPHIL Neutrophil Granulocyte (Polymorphonuclear Leucocyte)

The essential function of these cells is protection against microbial infection by phagocytosis and killing. They are produced alongside red blood cells, platelets and monocytes from a common stem cell in the marrow.

Marrow Production – stained by a Romanowski method

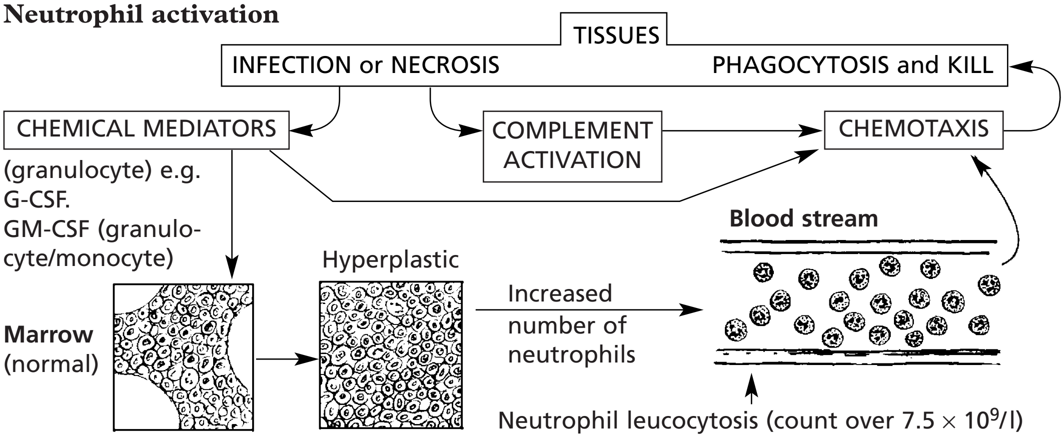


Note the nuclear changes progressing from large open nucleus and several nucleoli to the mature condensed multi-lobed state. The cytoplasm matures with the acquisition of specific granules.



An increase in the number of circulating neutrophils reflects an increased activity in the tissues at the site of an acute inflammatory reaction.

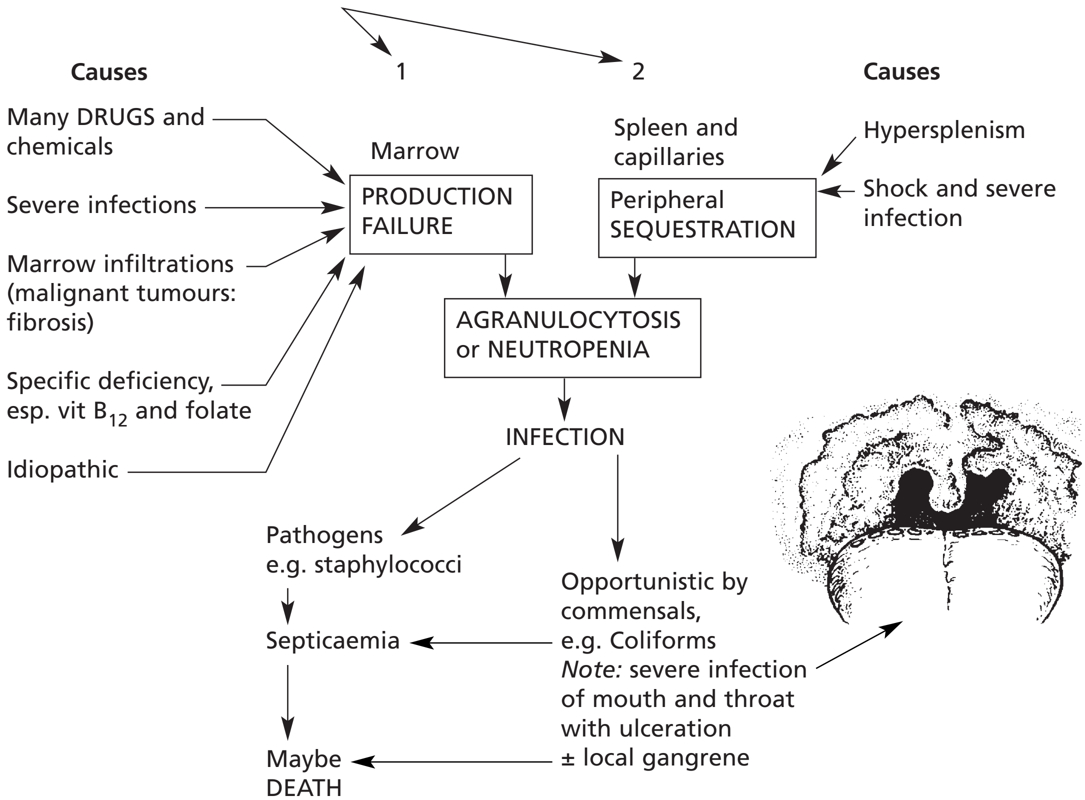
Neutrophil activation



DISORDERS OF NEUTROPHILS – AGRANULOCYTOSIS

Although a common finding in many bacterial infections, neutrophil leucocytosis does not occur in: (a) some acute bacterial infections, e.g. typhoid fever, brucellosis, (b) many chronic bacterial infection, e.g. TB, (c) most virus infections unless acute bacterial infection or necrosis occurs, (d) overwhelming infections with severe toxaemia.

In the **absence (agranulocytosis)** or **diminished numbers** of neutrophils – < 2.5 × 10/1 (2500/mm^3) increased susceptibility to infection results.
There are 2 **main mechanisms** which often co-exist.



Drugs may act in the following ways:

1. By direct dose related toxic effect, e.g. modern chemotherapeutic agents. → Marrow failure
2. By an immunological reaction, the drug acting as a **hapten**, e.g. amidopyrine. → Marrow failure
3. By an idiosyncratic action in sensitive subjects small doses are effective, e.g. chloramphenicol (compare aplastic anaemia, page 409). → Marrow failure

Drugs and chemicals may affect the production of all three marrow cell types together or in various combinations.

DISORDERS OF NEUTROPHILS

Disorders of neutrophil function

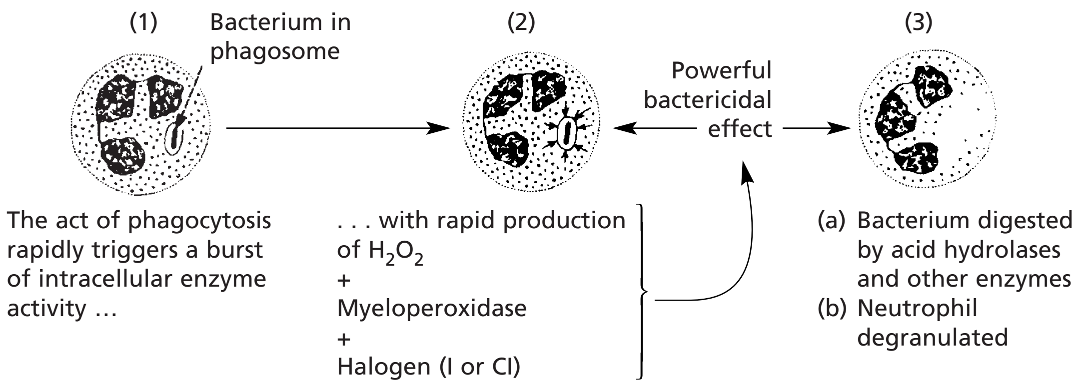
Divided into 3 groups: (1) chemotaxis, (2) microbial phagocytosis and (3) microbial kill.

Chemotaxis and phagocytosis may be defective due to:

(a) an intrinsic defect of the neutrophils e.g. leucocyte adhesion deficiency – reduction of B_2 integrin expression.
(b) plasma deficiency of chemotactic factors and opsonins – seen especially when there are deficiencies in the complement cascade.

Microbial kill fails when there is an intracellular enzyme defect e.g. in *chronic granulomatous disease* (CGD) and the Chediak–Higashi syndrome where the neutrophils contain abnormal giant granules.

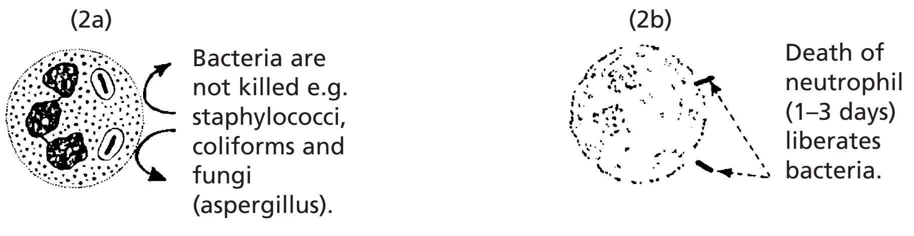
The normal sequence following phagocytosis is:



CHRONIC GRANULOMATOUS DISEASE (CGD)

It is a rare hereditary disorder in which the neutrophils have normal phagocytic function but are unable to kill certain bacteria. The disease is fully expressed only in males. It presents as multiple chronic abscesses and granulomas affecting skin, lungs, bones, spleen and liver.

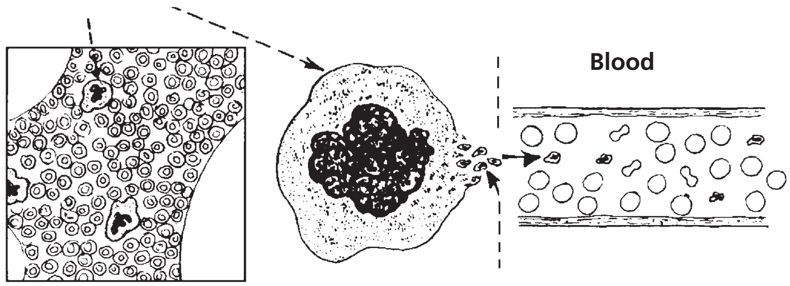
The rapid production of H_2O_2 is defective (in the neutrophils and also in macrophages due to deficiency of NADPH-oxidase).



About 2/3 of cases are X-linked (fully expressed in males): the remainder are recessive. The neutrophils are unable to reduce nitroblue tetrazolium (used as a diagnostic slide test).

PLATELETS AND COAGULATION

These small, non-nucleated discs, derived from the cytoplasm of the bone marrow megakaryocytes, are released into the blood stream by a budding process.



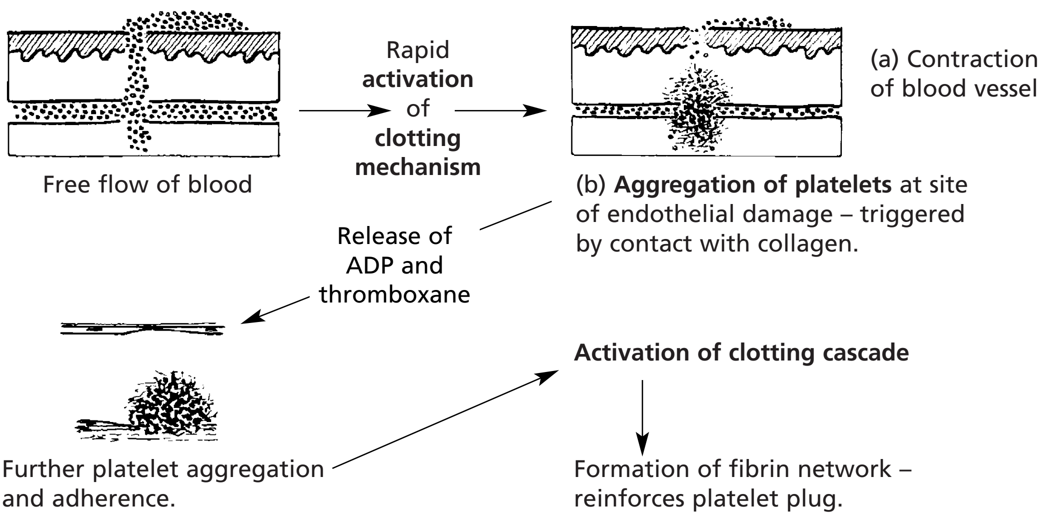
Count:
150–400 × 10^9/l
(150 000–400 000/mm^3)

Size: 1–3 μm

Platelets contain von Willebrand factor, adenosine diphosphate (ADP), vasoactive amines including serotonin (5HT) and histamine and phospholipid

Their main role is in preventing blood loss after injury.

e.g. skin wound.



ABNORMALITIES OF COAGULATION

Blood may (a) CLOT INSUFFICIENTLY or (b) CLOT EXCESSIVELY

HAEMORRHAGIC TENDENCY
– too few platelets (THROMBOCYTOPENIA)
  – excess destruction.
  – decreased formation.
– abnormal platelet function.
– deficiency of clotting factors.

THROMBOSIS
– too many platelets (THROMBOCYTOSIS).
– increased viscosity –
  e.g. in polycythaemia.
– due to deficiency of inhibitors
  of clotting factors.

DISORDERS OF PLATELETS

Disorders of the platelets include:
(a) deficiencies of number – thrombocytopenia – lead to bleeding tendency.
(b) defective function.

THROMBOCYTOPENIA

Although the normal platelet count ranges from 150–400 $\times$ 10^9/l, a risk of dangerous spontaneous haemorrhage is unusual unless the count falls below 30 $\times$ 10^9/l.
The causes of thrombocytopenia fall into two main groups:

1. **Deficient marrow production**	2. **Increased destruction**
Hypoplasia or aplasia of marrow	Platelets damaged by *drugs*, *immune mechanisms*
Replacement (e.g. leukaemia, fibrosis) of marrow	Platelets sequestered in *hypersplenism*
Dyshaemopoiesis (e.g. Vit B_{12} deficiency)	Platelets utilised in *coagulation disorders* (e.g. DIC)

Note: Marrow examination throws light on the possible mechanism.

In (1) megakaryocytes are reduced in number (except in vit. B_{12} deficiency)	In (2) megakaryocytes are increased and immature in an attempt to make good the platelet loss

PURPURA is the term used for disorders involving bleeding from capillaries, with the production of small petechial spots. Mild to moderate thrombocytopenia or defective platelet formation are the usual causes. Two examples are illustrative:

1.**Idiopathic thrombocytopenic purpura** is due to **auto-immune** destruction of platelets. Antibodies are directed against platelet membrane glycoproteins.
(a) **Acute:** mainly in children, provoked by viral infection: it is usually self-limiting in a few weeks.
(b) **Chronic:** mainly in young women with an insidious onset and lasting many years: splenectomy is often required (the spleen is the major site of platelet destruction).

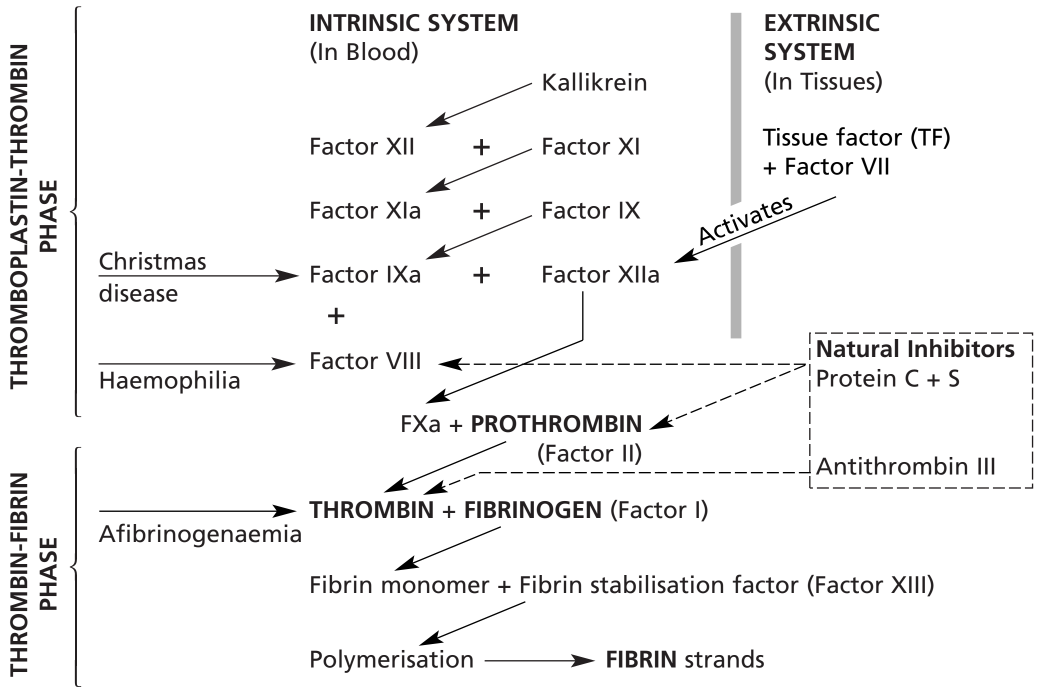
2. **Defective platelet functio**n has many forms – **von Willebrand's disease** (vWD) is the commonest. The gene encoding vWF is located on chromosome 12.
vWF is a large protein which potentiates the binding of platelets to subendothelial collagen and also acts as a carrier for coagulation factor VIII.

Diminished function or lack of vWF
↓ ↓
Diminished platelet adhesion — Diminished factor VIII activity
↓ ↓
HAEMORRHAGE

THROMBOCYTOSIS (increased platelet numbers) may occur in a mild form (with no clinical significance) reactive to a variety of disorders of chronic inflammation and cancer. Larger counts are seen in myeloproliferative disorders (e.g. essential thrombocytosis, chronic myeloid leukaemia) and are of serious clinical significance due to thrombosis.

THE COAGULATION CASCADE

The coagulation of blood is the result of conversion of **FIBRINOGEN** to **FIBRIN**, but the chemical pathway leading to this final phase is a complicated cascade in which inert coagulation factors are serially activated. At each step augmentation takes place.



Note: 'a' denotes activated form

The system contains several feed-back loops (not illustrated) which can inhibit the cascade at various levels.
Anti-thrombin III and the protein C/protein S system are powerful inhibitors preventing uncontrollable coagulation.
Vitamin K is required for the production of factors II, VII, IX and X. CALCIUM ions and phospholipids (mainly derived from platelets) are essential for many of the steps in thrombin production. Once thrombin is formed, it appears to stimulate several of the preceding reactions and also the polymerisation of fibrin.

Fibrinolytic System – This occurs following fibrin deposition as a protective mechanism against excess coagulation.

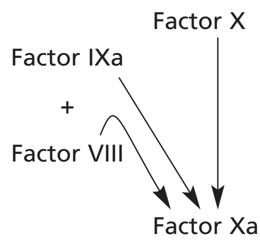


INHERITED DEFECTS OF COAGULATION

These are less common than acquired abnormalities, but are of considerable importance.

HAEMOPHILIA A

Haemophilia is due to deficiency of Factor VIII – an essential cofactor in the activation of Factor X in the intrinsic system.



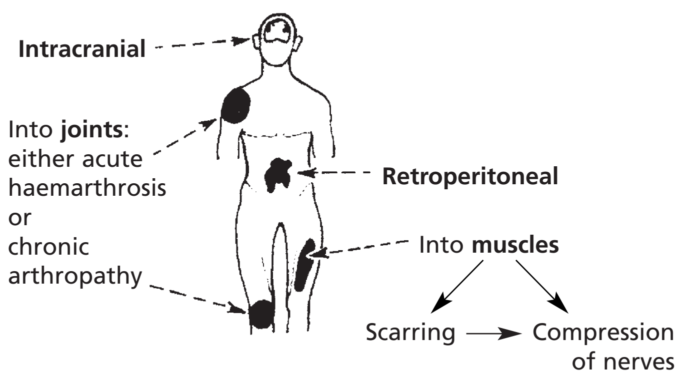
Factor VIII is encoded by a gene on the long arm of the X chromosome – haemophilia is inherited as an X-linked recessive, i.e. almost all patients are male. Their mothers are usually carriers, but about 30% of cases are due to new mutations. Around 1 in 10 000 is affected.

Clinical Features

The severity depends on the levels of Factor VIII.

		Level of Factor VIII
Severe:	Frequent spontaneous bleeding.	<2% of normal
Moderate:	Bleeding after minor trauma – rarely spontaneous.	2–10%
Mild:	Bleeding severe only after major trauma or surgery.	10–50%

Important sites of bleeding are:



Note: In the past, the use of virus infected Factor VIII in treatment has caused HIV (AIDS) and Hepatitis C infection. Similar concerns apply to variant CJD (p.555).

HAEMOPHILIA B (Christmas disease)

This is due to deficiency of Factor IX – also carried by a gene on the X chromosome. The clinical features are similar, but the prevalence is lower (1 in 30 000 males).

Rarely deficiencies of other coagulation factors are seen, e.g. fibrinogen, Factor XI and Factor V.

They are treated by infusion of the appropriate factors.

ACQUIRED DEFECTS OF COAGULATION

This large and heterogeneous group of conditions includes:

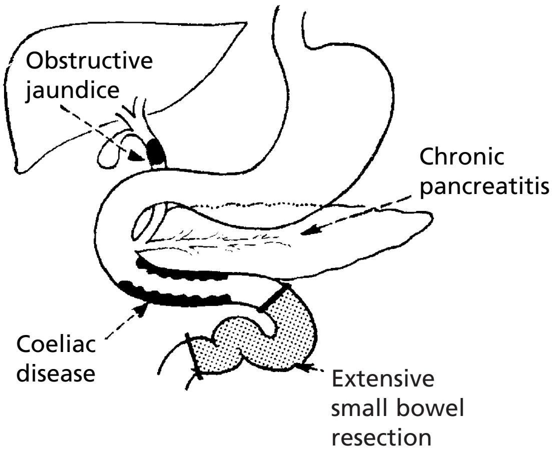
VITAMIN K DEFICIENCY
Vitamin K, a fat soluble vitamin, is essential for synthesis of Factors II, VII, IX and X in the liver. Deficiency leads to spontaneous bleeding, e.g. into skin and mucous membranes, and failure of blood clotting.

In **adults**, deficiency may be due to

(a) MALABSORPTION (particularly of fat)

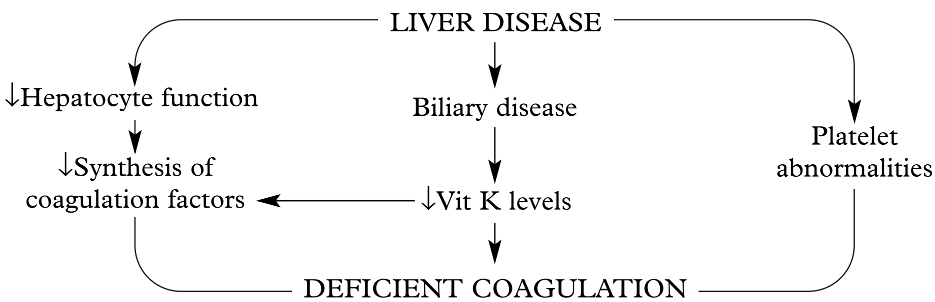
(b) DIETARY DEFICIENCY – rare – Vitamin K is widely distributed, e.g. in green vegetables, oils.

(c) INHIBITION – by COUMARIN anticoagulants, e.g. WARFARIN.



In **neonates**, vitamin K deficiency leads to bleeding – from GI tract and bruising. Breast milk contains little vitamin K – the disorder is uncommon in those receiving bottled milk. A severe deficiency may be seen in infants whose mothers took anticoagulants or anticonvulsants.

LIVER DISEASE
The bleeding tendency in these patients is multifactorial.



This complicates bleeding, e.g. from OESOPHAGEAL varices.

'ACQUIRED HAEMOPHILIA'
Rarely, antibodies develop which block the effects of serum coagulation factors, especially Factor VIII. This may be idiopathic or follow auto-immune disease or drug treatment.

Disseminated Intravascular Coagulation (DIC) (see next page).

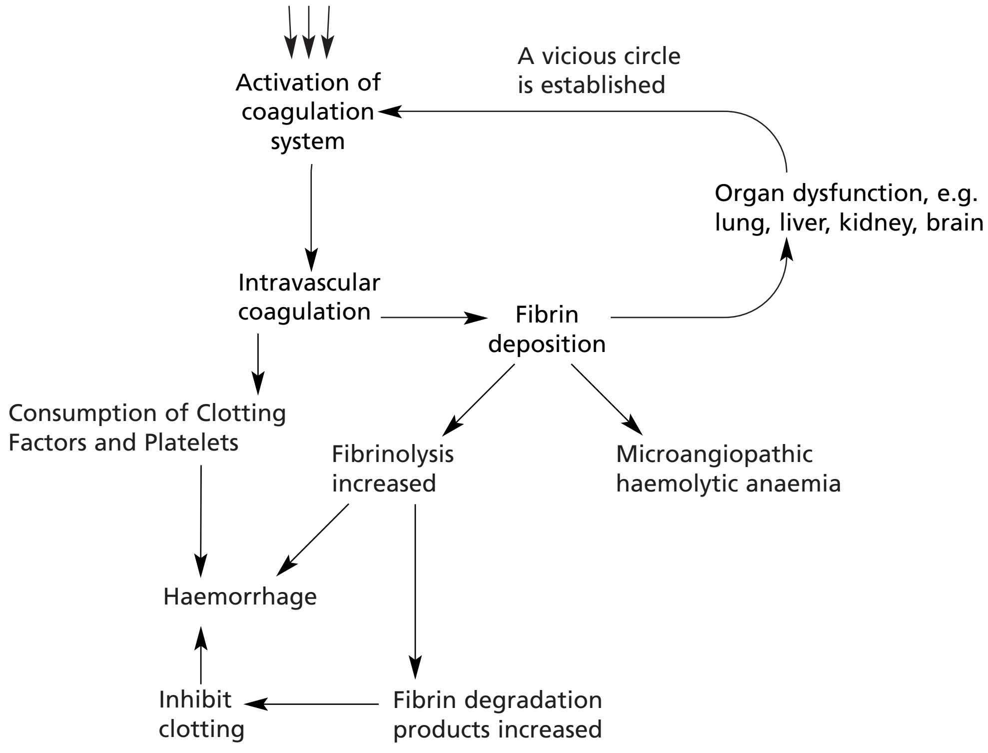
DISSEMINATED INTRAVASCULAR COAGULATION

In this disorder the coagulation system is activated, but the consumption of platelets and clotting factors which follows leads to a paradoxical bleeding tendency.

There are numerous causes:

(a) SEPTICAEMIA – especially gram negative septicaemia,
– in meningococcal infections.
(b) SHOCK e.g. following severe burns.
(c) OBSTETRIC DISORDERS e.g. abruptio placentae, amniotic embolism, eclampsia.
(d) MALIGNANCY – especially acute promyelocytic leukaemia and mucin secreting adenocarcinomas (e.g. of stomach).
(e) IMMUNOLOGICAL DISORDERS e.g. autoimmune diseases,
– incompatible blood transfusion.

The basic mechanism is as follows:



Patients frequently develop renal and hepatic failure and 'shock lung' [e.g. in the haemolytic uraemic syndrome (HUS) which is often associated with toxigenic *E.coli* infection – especially *E.coli* 0157 (see p.314)].

THROMBOPHILIA – THROMBOTIC DISORDERS

The major types, causes and effects of thrombosis are discussed on pages 159–163.

Recently, a group of inherited disorders has been discovered where deficiency of NATURAL ANTICOAGULANTS leads to an increased risk of venous thrombosis. This may be deep venous thrombosis in the lower limbs or visceral, e.g mesenteric veins. There is also an increased risk of pulmonary embolism.

The main forms are:

(a) **ANTITHROMBIN DEFICIENCY**
Antithrombin, a member of the SERPIN group of **Ser**ine **p**rotease **in**hibitors, is synthesised in the liver. It blocks the action of F IXa, F Xa, F XIa and thrombin. Deficiency is due to mutation of a gene on the long arm of chromosome 1 – the effects depend on the exact type of mutation. The prevalence is around 1 in 20 000.

Note: **Heparin**, the anticoagulant, acts by enhancing the action of antithrombin.

(b) **PROTEIN C DEFICIENCY**
This is a Vitamin K dependent protein, synthesised in the liver. Together with protein S it blocks the action of Factor Va and Factor VIIIa. Around 1 in 15–30 000 is affected. In addition to deep thrombosis, patients also get superficial thrombophlebitis.

(c) **PROTEIN S DEFICIENCY**
This protein is secreted by the liver, platelets and endothelial cells. Its function is to bind with protein C to inhibit Factors Va and VIIIa.

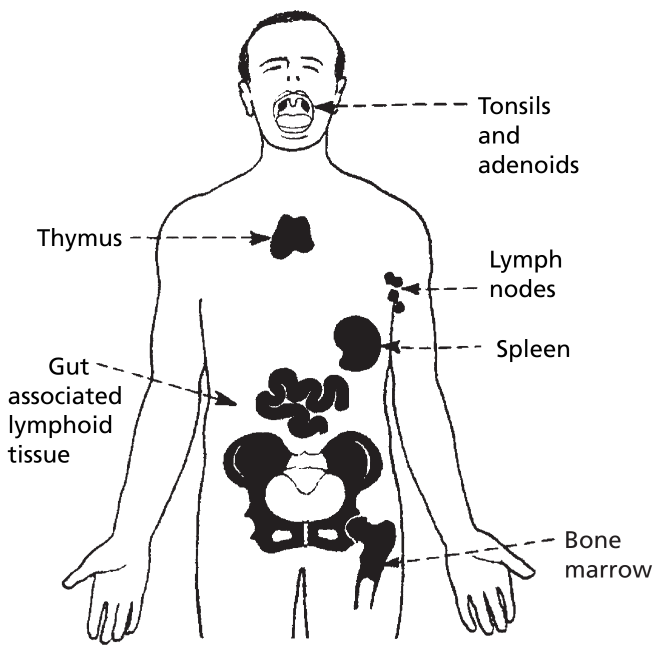
(d) **ACTIVATED PROTEIN C RESISTANCE**
This is an inherited disorder where a mutation affects the Factor V gene. The protein is resistant to the effects of protein C – simulating protein C deficiency.

The possible role of minor deficiencies of these genetic factors in the more common forms of thrombosis is not yet established. The well known risk factors for thrombosis are listed below.

Acquired risk factors for thrombosis include:

Arterial	**Venous**
ATHEROMA	IMMOBILITY
SMOKING	TRAUMA/SURGERY
HYPERTENSION	MALIGNANCY
MYELOPROLIFERATIVE DISORDERS	ORAL CONTRACEPTIVES
	OBESITY

THE LYMPHOID SYSTEM



The lymphoid organs are principally involved in:

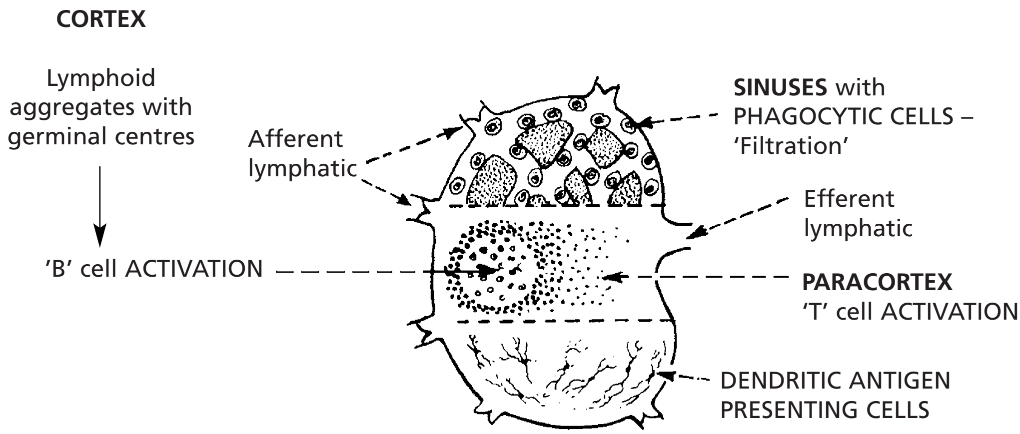
(a) Production and maturation of lymphocytes – thymus (T cells) and bone marrow (B cells).

(b) Antigen presentation and the immune response.

(c) 'Filtration' and phagocytosis of micro-organisms and particulate material.

LYMPH NODES

The basic structure reflects the main functions.



LYMPHADENOPATHY

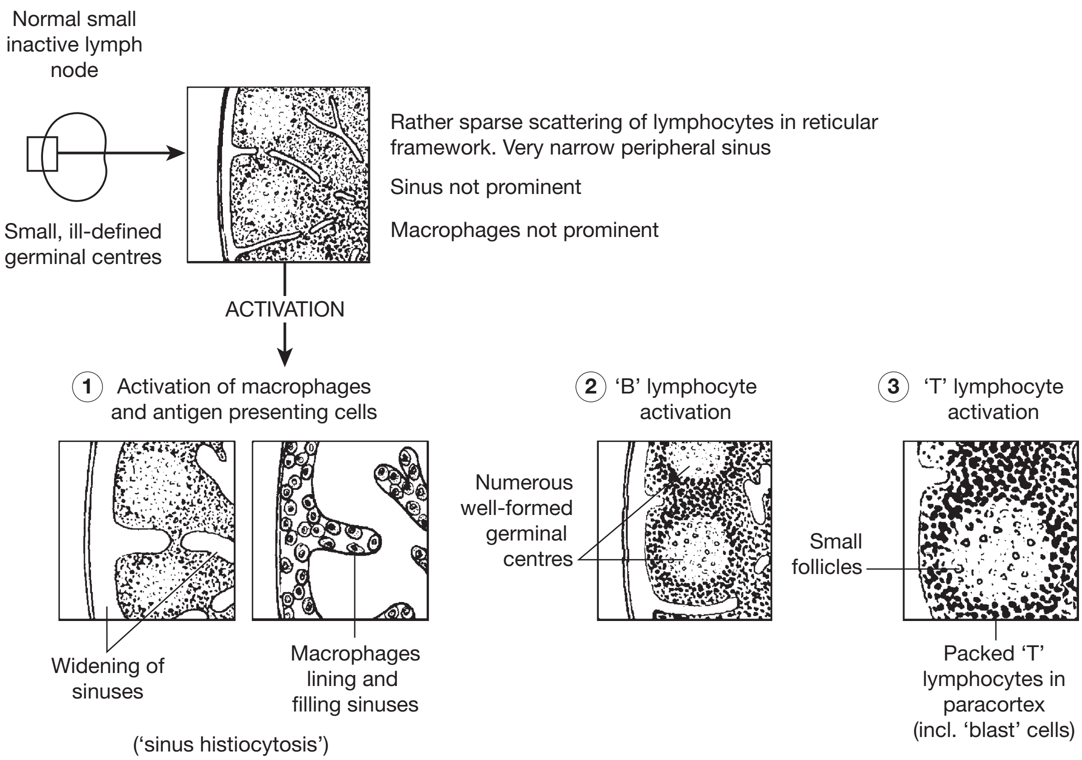
Lymph node enlargement may be **localised** or **generalised**. It may be due to:

(a) reactive hyperplasia e.g. – infection by bacteria or viruses,
– particulate material,
– immune stimulation e.g. Rheumatoid arthritis,
– draining degradation products from a cancer.

(b) due to neoplasia e.g. – secondary deposits of carcinoma,
– primary lymphoid tumours.

REACTIVE HYPERPLASIA

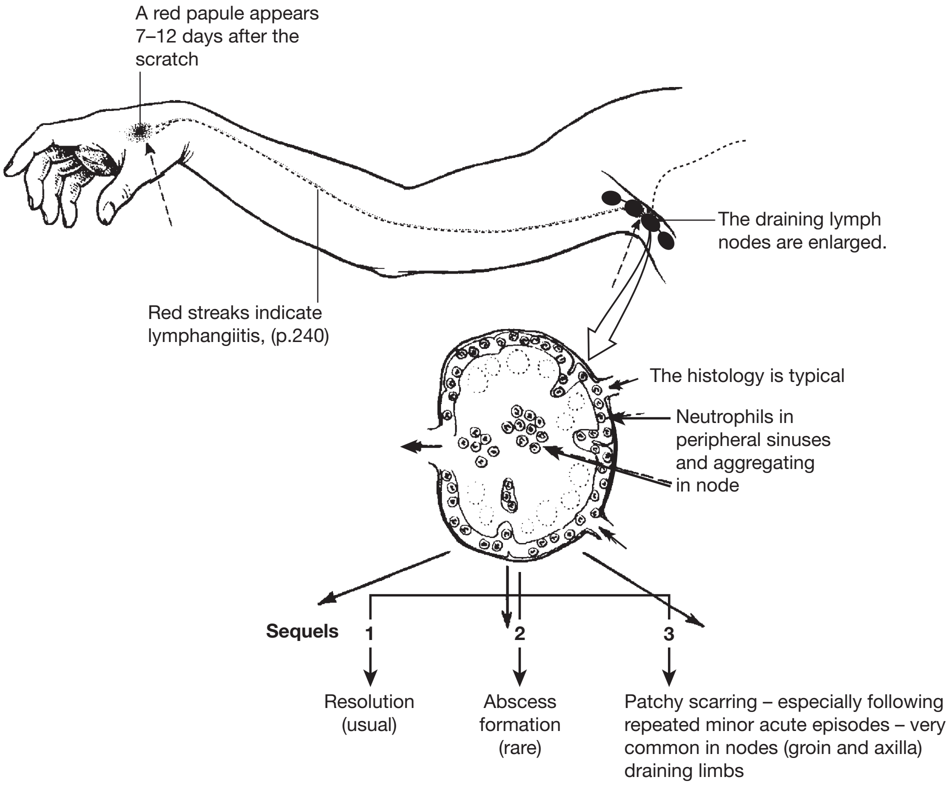
Several patterns are seen.



LYMPHADENOPATHY – INFECTIONS

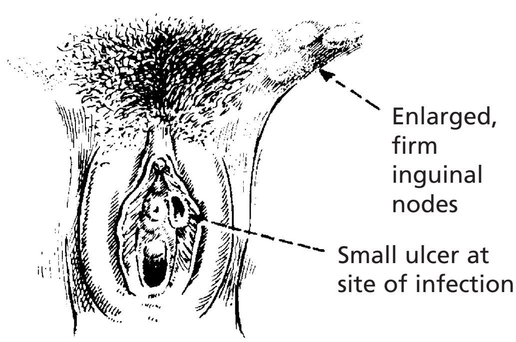
ACUTE BACTERIAL LYMPHADENITIS

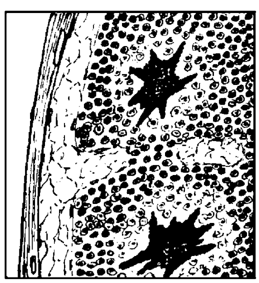
This is seen draining an infected area.



CAT SCRATCH DISEASE

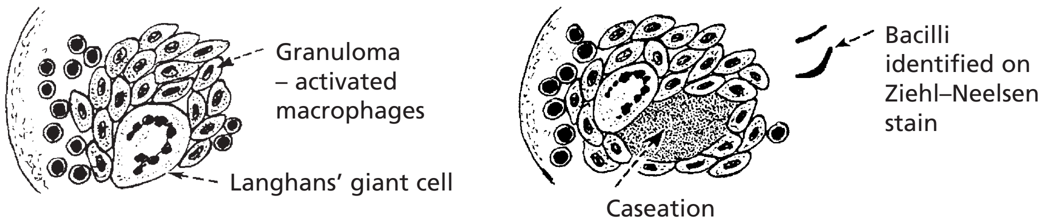
This infection by a bacterium *Bartonella henselae* follows scratching by an infected cat. Similar histology is seen in lymphogranuloma venereum, caused by *Klebsiella granulomatis*. A small transient painless genital ulcer is followed by inguinal lymphadenopathy (figure). The diagnosis can be confirmed by the Frei test (injection of purified chlamydial antigen stimulates a delayed hypersensitivity reaction).





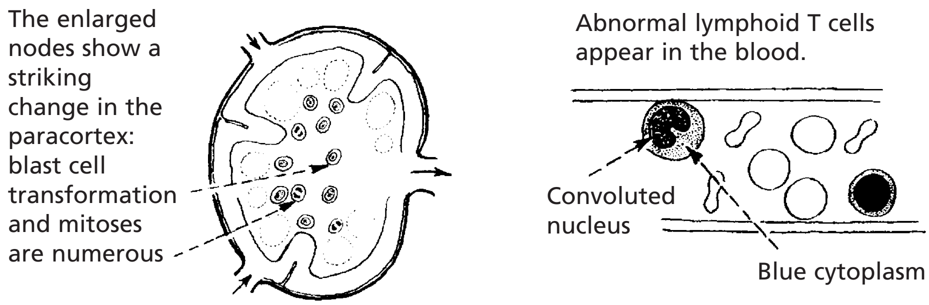
LYMPHADENOPATHY

TUBERCULOSIS is associated with a granulomatous response (p.42), often with caseation; this is due to delayed type sensitivity.

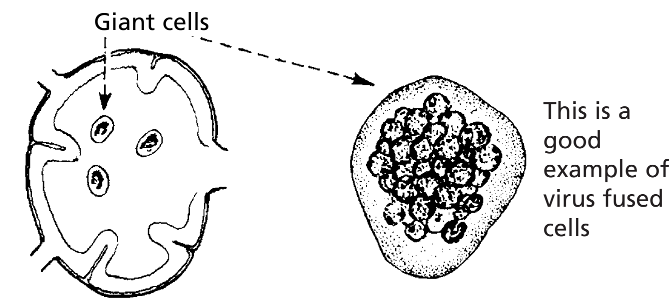


VIRAL LYMPHADENITIS – Many infections induce paracortical hyperplasia – with activation of T cells.

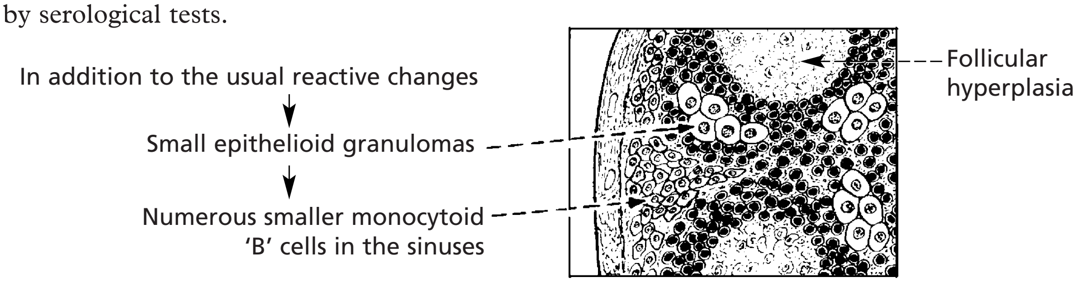
In **GLANDULAR FEVER** (Infectious mononucleosis), an infection by Epstein–Barr virus of young adults, the cervical lymph nodes are particularly involved.



In **MEASLES**, the reactive nodes and lymphoid tissues generally contain unusual, multinucleate **giant cells** (Warthin–Finkeldey).



In **TOXOPLASMOSIS**, a protozoal disease (*Toxoplasma gondii*) which may cause serious damage to the fetus or neonate and present with lymph node enlargement in the adult, the histological appearances in the node may indicate the aetiology. The diagnosis is confirmed by serological tests.



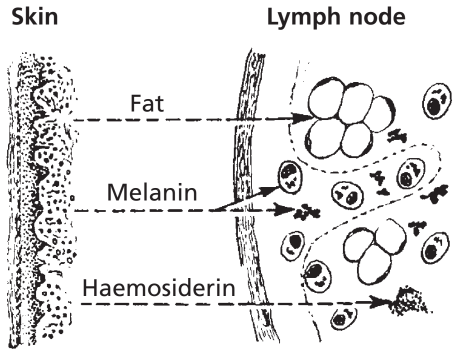
LYMPHADENOPATHY – NON-INFECTIVE CAUSES

FOREIGN MATERIAL
Lymph nodes to which foreign particulate material drains often show marked enlargement due to accumulation of macrophages which have ingested the foreign material.

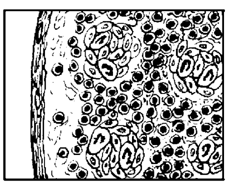
For example:
– carbon and silica in hilar lymph nodes
– silicone, e.g. in axillary lymph nodes in patients with prosthetic joints and breast implants.

CHRONIC SKIN DISEASE (so-called dermatopathic lymphadenopathy) e.g. psoriasis, eczema and mycosis fungoides (p.435).

The following may be seen lying free and in macrophages:
Fat
Melanin – from damaged skin
Haemosiderin – from minor bleeding in skin



SARCOIDOSIS
In this disease of unknown aetiology non-caseating granulomas are seen.

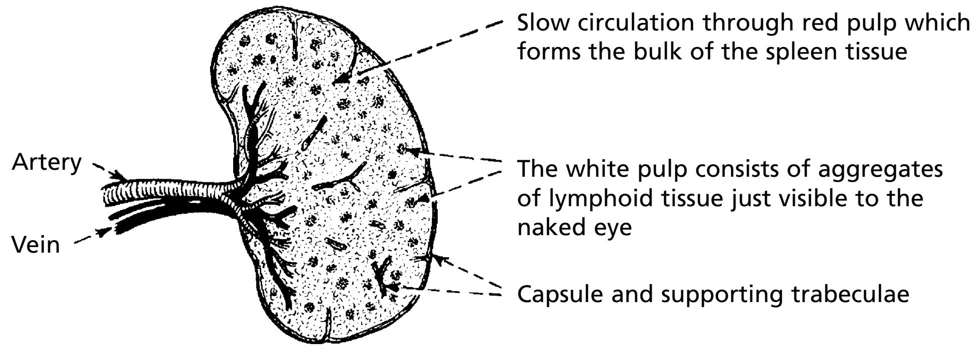


The appearances clearly resemble tuberculosis, but the granulomas remain discrete and there is no caseation.

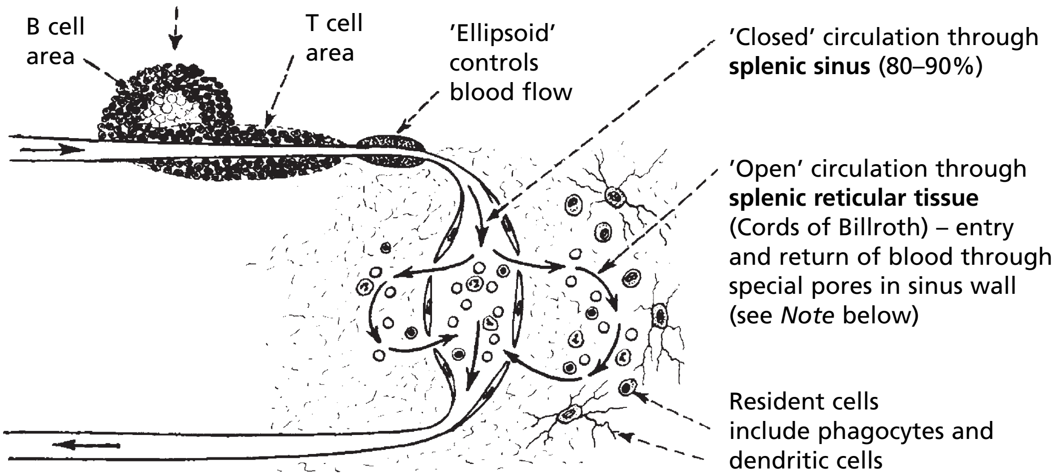
Sarcoid type granulomas are also seen in the lymph nodes of patients with other granulomatous diseases, e.g. Crohn's disease and in lymph nodes draining tumours.

SPLEEN

The spleen is responsible for filtering the blood, phagocytosing debris and generating an immune response.
Normal average weight – 150 g.



Microscopic appearance
Lymphoid aggregate – mediates IMMUNE RESPONSE.



The red pulp is the site of filtration and phagocytosis of the following:

1. Worn out cells and cell debris – especially blood cells but also cell debris derived from the body generally
2. Microbes and their toxins
3. Abnormal or excess material derived from metabolic processes.

Note: The special pores allowing re-entry of RBCs to the circulation have a 2 μm aperture: abnormal RBCs (e.g. spherocytes) cannot pass through and are trapped.

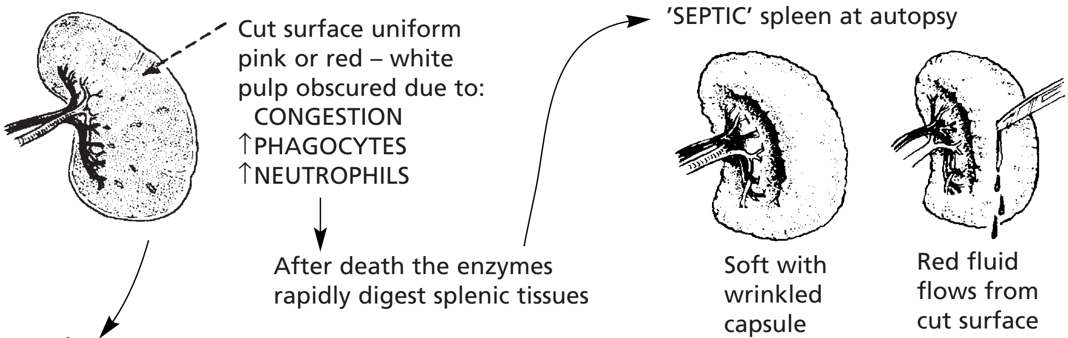
SPLENOMEGALY

Enlargement of the spleen is an important and common clinical sign. Increase in the red pulp due to increased numbers of phagocytes and/or increased numbers of blood cells is the major component. In chronic infections, hyperplasia of the lymphoid tissue contributes.

Enlargement is associated with:
1. INFECTIONS
2. CIRCULATORY DISTURBANCES
3. DISORDERS OF THE BLOOD
4. NEOPLASIA – primary and secondary
5. STORAGE DISEASES and DEGENERATIONS.

1. INFECTIONS

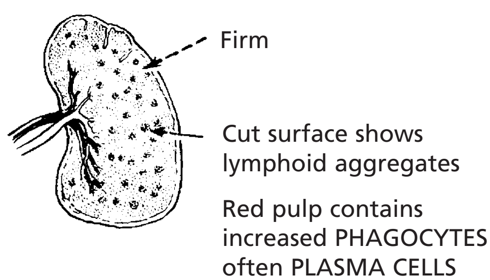
In acute systemic bacterial infections the spleen shows slight to moderate enlargement (200–400 g).



Sequels

(a) Resolution as infection resolves.
(b) Occasionally spreads through capsule to adjacent tissues, with or without abscess formation.
(c) Only extremely rarely does abscess formation occur within the spleen.

In non-pyogenic and chronic infections, there may be moderate enlargement.

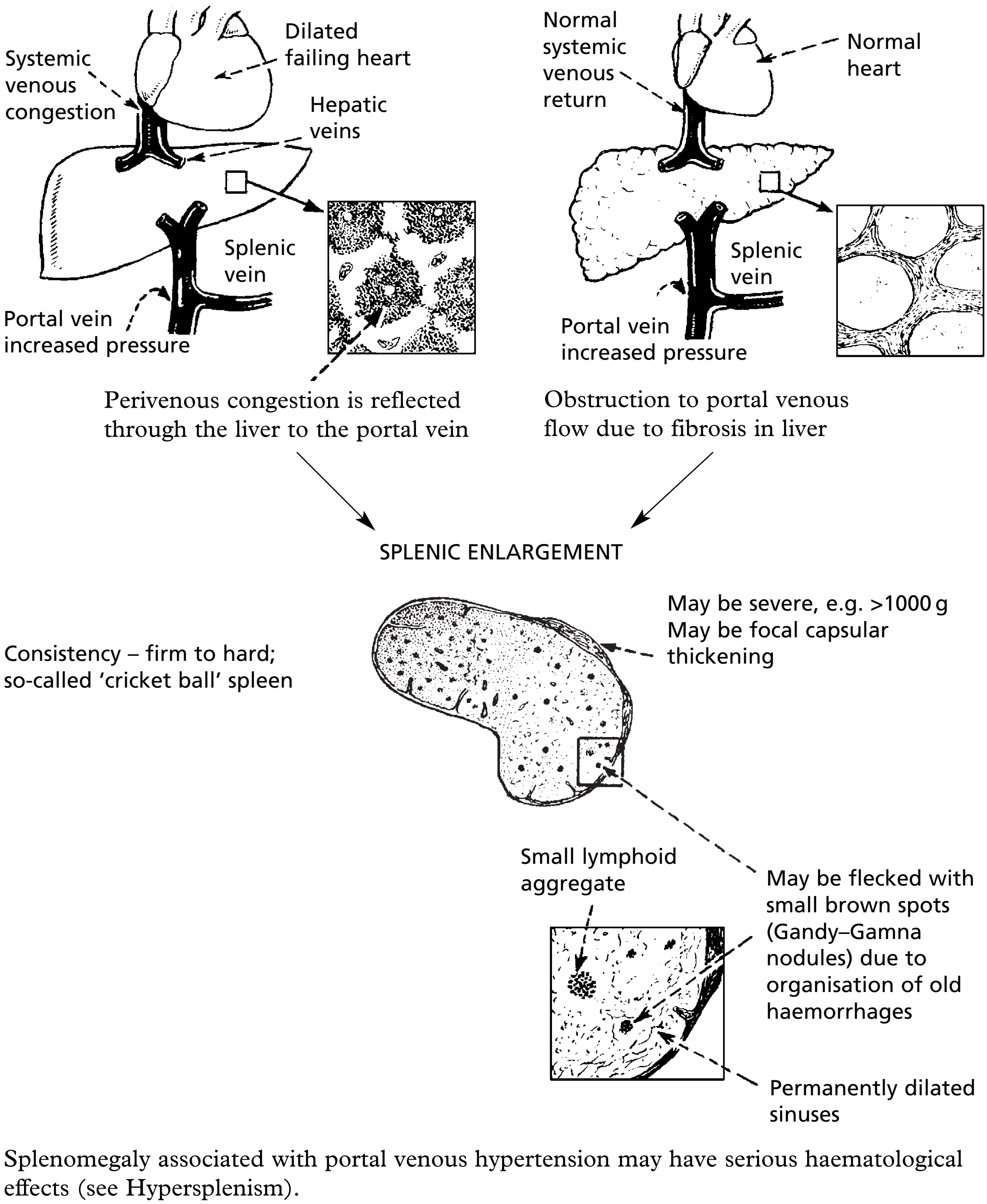


Examples: Infective endocarditis
Tuberculosis
Typhoid fever
Infectious mononucleosis
Brucellosis
In protozoal diseases – malaria and kala-azar – there is often massive enlargement

SPLENOMEGALY

2. **CIRCULATORY DISTURBANCES**
Congestive splenomegaly occurs in two main conditions:

(1) **Congestive cardiac failure** (2) **Hepatic cirrhosis**



Splenomegaly associated with portal venous hypertension may have serious haematological effects (see Hypersplenism).

SPLENOMEGALY

3. **DISORDERS OF THE BLOOD**

Splenic enlargement is associated with blood disorders in two main circumstances:

1. **Splenic enlargement causing blood disorders (hypersplenism).**

ENLARGED SPLEEN from any cause, but particularly in cases of **portal hypertension** → Increased capacity for sequestration of blood cells → Reduction in circulating blood cells, i.e. *anaemia, leucopenia, thrombocytopenia,* separately or together, i.e. **pancytopenia** → Marrow hyperplasia

2. **Blood disorder causing splenic enlargement**

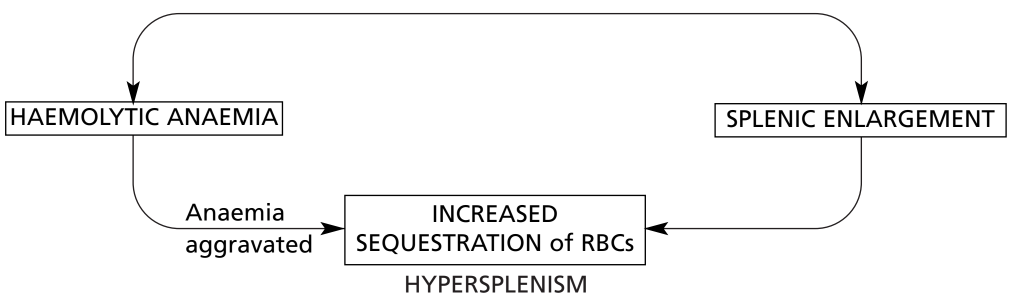
(a) Production of abnormal blood cells, e.g. in haemolytic anaemias: idiopathic thrombocytopenia (antibody coated platelets) → Increased demand on sequestration function of spleen → Increase in spleen size

(b) leukaemias and lymphomas → Infiltration of spleen by neoplastic cells → Increase in spleen size

(b) leukaemias and lymphomas → Increased sequestration of abnormal cells → Increase in spleen size

(c) In chronic marrow failure due to fibrosis or secondary tumour infiltration → Resumption by spleen of fetal blood forming role (extramedullary haemopoiesis) → Increase in spleen size – may be massive (500–2 000 g)

Sometimes these two processes combine to form a vicious circle.

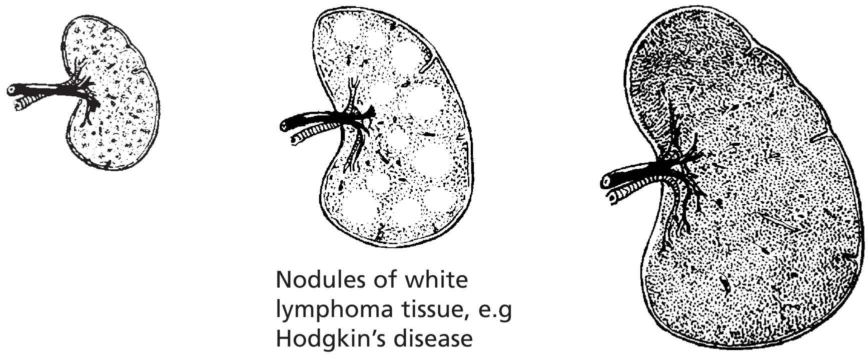


SPLENOMEGALY

4. **NEOPLASIA**

(a) PRIMARY – primary tumours of the spleen are rare with only occasional primary splenic lymphomas occurring.

(b) SECONDARY – Splenic involvement by lymphoma and leukaemia is far commoner than by metastatic carcinoma.



Splenic enlargement may be a feature of Langerhans cell histiocytosis.

5. **STORAGE DISEASES AND DEGENERATIONS**
The diseases associated with this type of enlargement are rare.

Examples are:

Amyloidosis (see pp.22–24)
Lipid storage diseases (see p.21) including Gaucher's disease, Niemann–Pick disease and Tay–Sachs disease.

Some disorders of glycogen storage.

DISEASES OF THE SPLEEN – MISCELLANEOUS

HYPOSPLENISM

Hyposplenism is not usually a cause of major disability. It occurs following splenectomy and in cases of splenic atrophy.

The effects are considered under two main headings:

1. **On the cells of the blood**

Loss of splenic sequestration function

↓

Deficiency in disposal of abnormal cells

→ Red cell series:
(a) increased acanthocytes
(b) increased Howell–Jolly bodies
(c) increased number of iron-containing cells

→ Neutrophils: may be leucocytosis

→ Platelets: may be thrombocythaemia

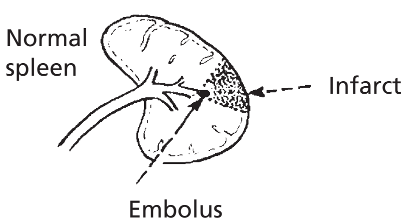
(Neutrophils and platelets:) Seen especially after splenectomy – usually not permanent

2. **On resistance to infection**

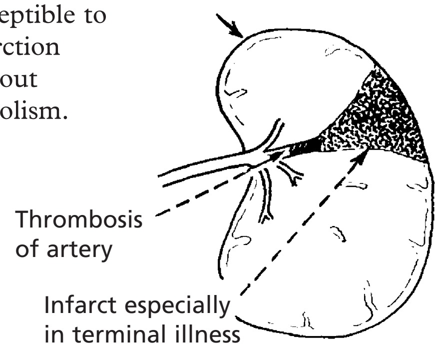
Loss of filtration of bacteria from blood → **Septicaemia** – especially caused by *Streptococcus pneumoniae* – young children are particularly susceptible and are vaccinated against this.

INFARCTION

(i) Embolism causing infarction is not uncommon but usually clinically unimportant.

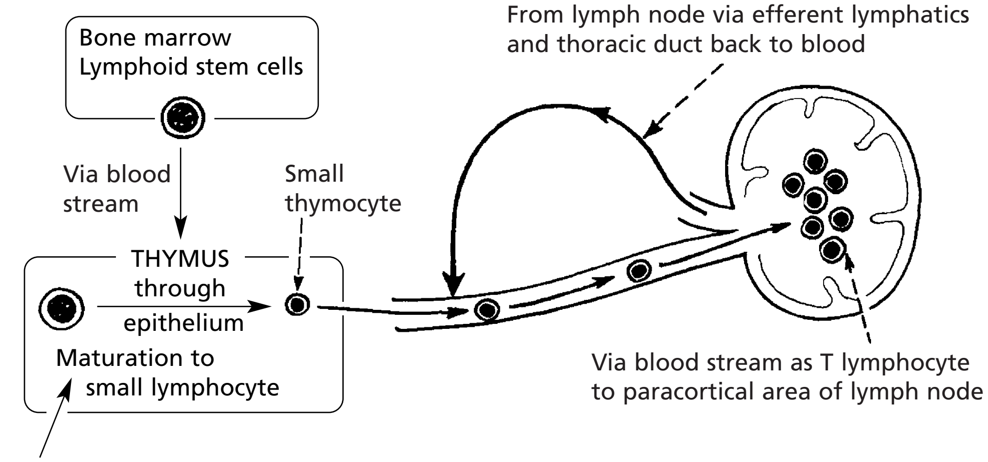


(ii) Enlarged spleens are particularly susceptible to infarction without embolism.



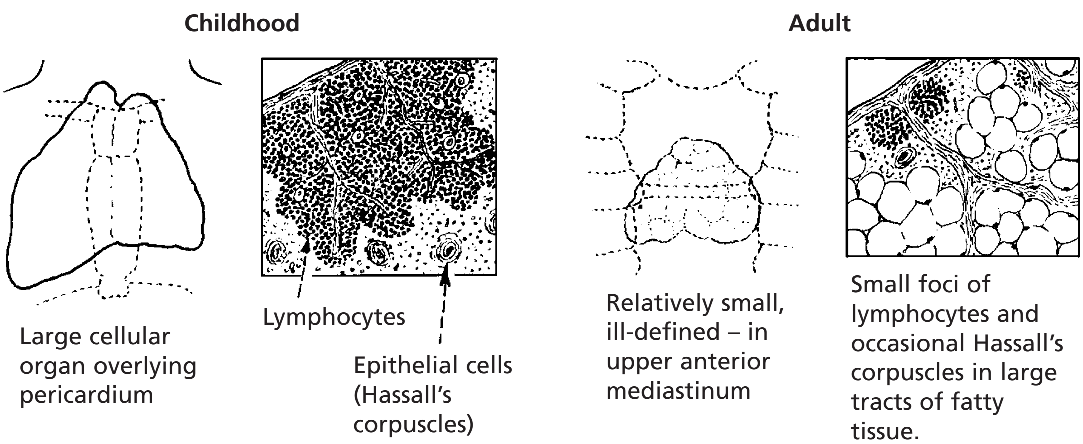
THYMUS

This 'primary' lymphoid organ is concerned with the development and maturation of T lymphocytes which are then distributed to the lymphoid tissues and to the circulating pool.



Mechanism – stimulation by hormones formed locally by thymic epithelial cells.

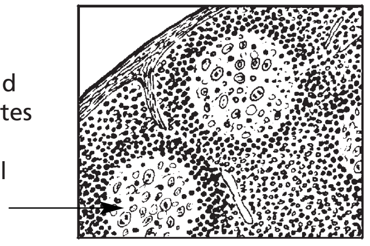
This activity is maximal in the fetal and childhood stages. Involution is rapid after puberty.



Congenital thymic aplasia or hypoplasia
The resulting T cell deficiency is associated with disordered cell-mediated immune response.

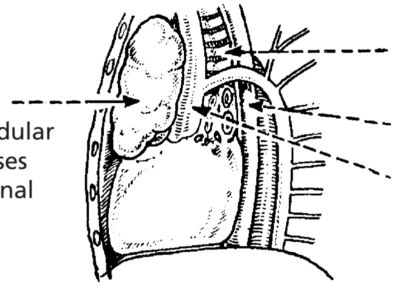
THYMUS

Thymic hyperplasia
This is associated with a number of conditions:



Auto-immune disorders,
e.g. Systemic lupus erythematosus
Addison's disease
Thyrotoxicosis
Pancytopenia
and *NB* MYASTHENIA GRAVIS

Thymic tumours
Thymomas are rare epithelial tumours: with an admixture of lymphoid cells: they rarely metastasise. A small number are carcinomas. They may have auto-immune associations similar to thymic hyperplasia.



Other primary tumours arising in the thymus are;
(1) T cell lymphoblastic lymphomas (adolescent males)
(2) Hodgkin's disease.
(3) Mediastinal large 'B' cell lymphoma
(4) Germ cell tumours (e.g. teratoma).
(5) Carcinoids.

The thymus in Myasthenia Gravis (MG)
MG is a disease of voluntary muscles in which weakness is the main feature. The association with the thymus is striking in that 80% of all patients with MG have either thymic hyperplasia or thymoma.

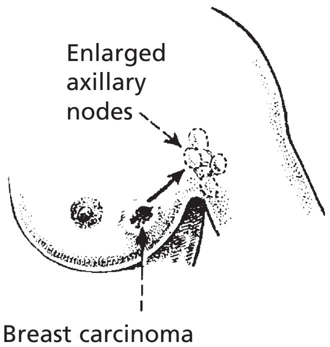
Follicular hyperplasia (80%) – seen especially in young females.
Thymoma (20%) – seen especially in middle aged males.
The results of thymectomy in MG patients are very unpredictable.

The detailed pathological changes in MG and the mechanisms by which the thymus is linked with the disease are described on pages 109, 614.

NEOPLASTIC LYMPHADENOPATHY

Lymph node enlargement may be due to
(a) Invasion by SECONDARY TUMOURS – especially CARCINOMAS –
or (b) Primary lymphoid tumours – LYMPHOMAS.

SECONDARY TUMOUR invasion
Carcinoma of the breast e.g.

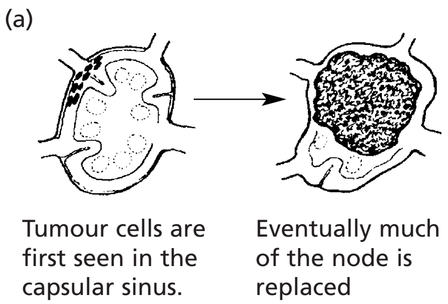


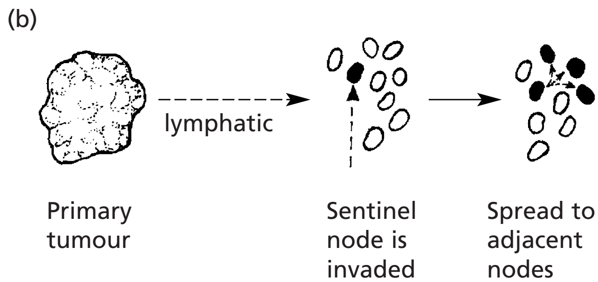
Note:

(i) The nodal enlargement is not necessarily due to secondary tumour.

Reactive hyperplasia is also common in nodes draining tumours especially if there is ulceration. The distinction between these 2 causes of node enlargement can only be made with certainty by **histological examination.**

(ii) The invasion of a group of nodes occurs in a step-wise fashion: a single node (the SENTINEL node) is invaded initially and spread to adjacent nodes follows.





Identification of the sentinel node may be required in the investigation of breast cancer and malignant melanoma.

LYMPHOMAS
Lymphomas are malignant tumours derived from lymphoid cells. They may arise within lymph nodes or at other sites (extra-nodal lymphomas).

Classically, they are divided into 2 main groups.

(a) Hodgkin's disease 20–25%
– almost always of lymph node origin.
– characterised by the presence of Reed–Sternberg cells.

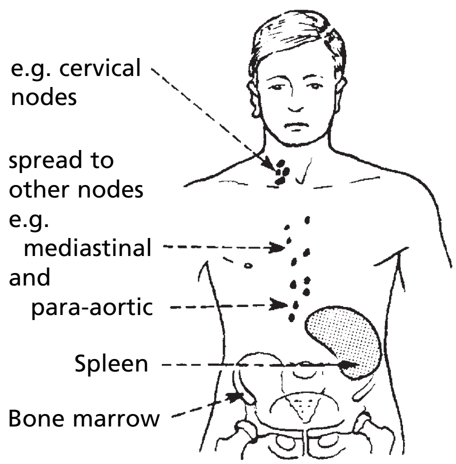
(b) Non-Hodgkin's disease 75–80%
– three-quarters arise in lymph nodes

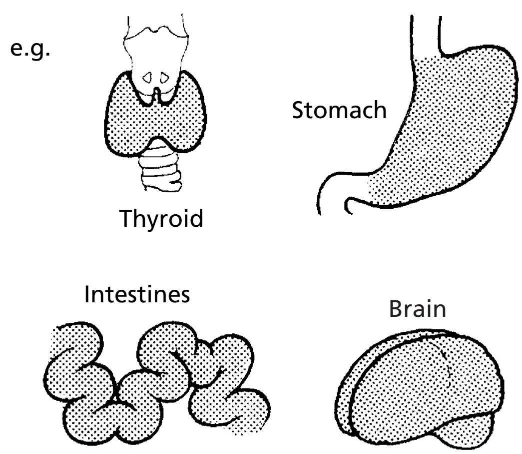
In recent years, modern immunocytochemical, molecular biological and cytogenetic techniques have been applied to the study of lymphomas. The traditional division between Hodgkin's and non-Hodgkin's lymphoma has been challenged but remains of major clinical importance.

NON-HODGKIN'S LYMPHOMAS

These tumours mainly affect middle aged to elderly patients.

They may arise
(a) Within lymph nodes or (b) in extra-nodal sites.



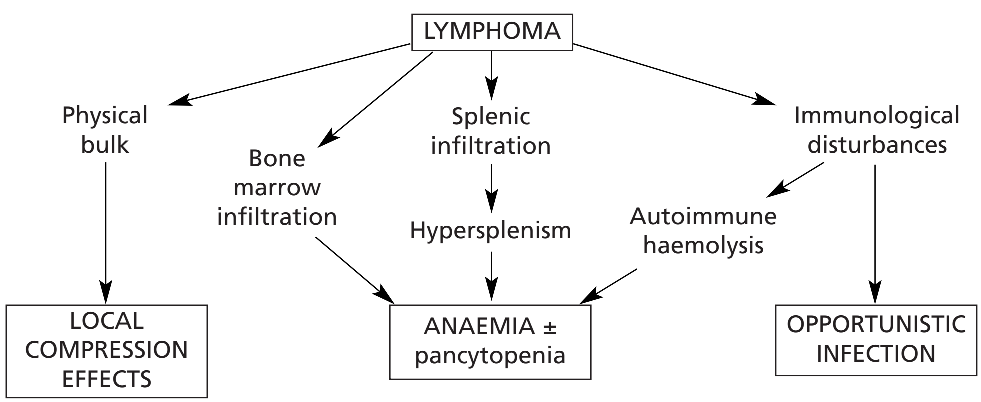


DEGREE OF MALIGNANCY
The natural history tends to separate lymphomas into two main groups which have links with the morphological appearances.

1. *Low grade malignancy* associated with well differentiated relatively inactive cell types,
– progress of years.

2. *High grade malignancy* associated with primitive actively proliferating cells,
– progress over weeks or months.
Tend to respond well to chemotherapy.

PATHOLOGICAL COMPLICATIONS



NON-HODGKIN'S LYMPHOMAS

Classification

This is a confusing area. Traditional classifications relied on morphology alone. The World Health Organisation Classification (2008) which includes immunohistochemistry and genetic data is now generally accepted. A simplified version follows:

NON-HODGKIN's LYMPHOMAS

B CELL (> 90%)

a) High Grade Tumours
   Diffuse large B cell lymphoma.
   Burkitt's lymphoma.

b) Low Grade Tumours
   Small lymphocytic lymphoma
   (equivalent to B-CELL, p.442).
   Lymphoplasmacytic lymphoma.
   Mantle cell lymphoma.
   Follicular lymphoma.
   Extranodal marginal zone B-cell lymphoma
   Myeloma/Plasmacytoma.

T CELL (< 10%)

Anaplastic large cell lymphomas
(some do not express T cell markers).

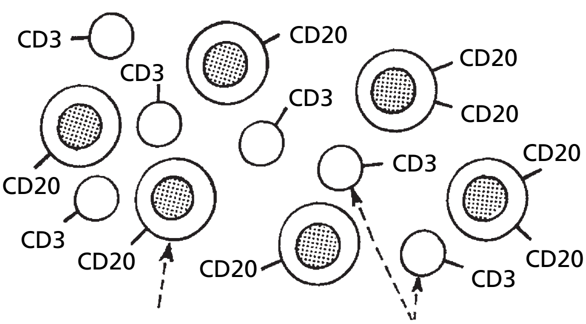
T cell prolymphocytic leukaemia
Peripheral T cell lymphoma.
Adult T cell leukaemia.
Angioimmunoblastic T cell lymphoma.
Enteropathy-type T cell lymphoma.
Mycosis fungoides (skin).

According to this classification each type is considered separately for treatment purposes.

The classification relies on cell surface markers which distinguish the B and T cells and their subsets. B and T cell monoclonality can be detected by gene rearrangements, and some types of lymphoma have characteristic translocations.

Subtyping of lymphoma

IMMUNOHISTOCHEMISTRY



Diffuse large B cell lymphoma – the cells express B cell markers, e.g. CD20

Frequently small reactive T cells are seen – they express CD3

MOLECULAR GENETIC ANALYSIS

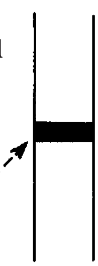
In B cell differentiation different immunoglobulin genes are found by gene rearrangements, while in T cell differentiation a similar process occurs with T cell antigen receptors (p.92).

In a polyclonal (reactive) population many different genes are found.



On DNA gel, many different bands.

In a monoclonal population the cells contain the same gene.



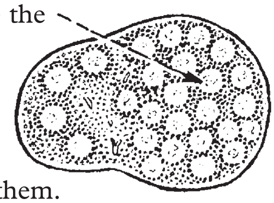
One strong monoclonal band.

NON-HODGKIN'S LYMPHOMAS

FOLLICULAR LYMPHOMA

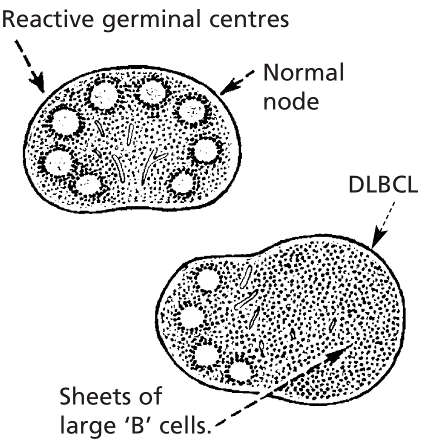
This is one of the commonest forms – a 'B' cell lymphoma.

The neoplastic follicles are the malignant equivalent of normal germinal centres.



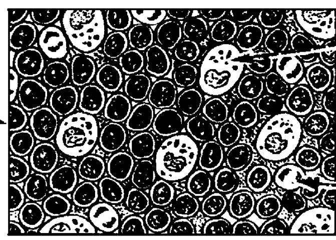
The tumour cells express the anti-apoptosis gene bcl–2 which immortalises them. There is often a translocation t (14;18) which joins the bcl–2 gene to the immunoglobulin heavy chain gene.

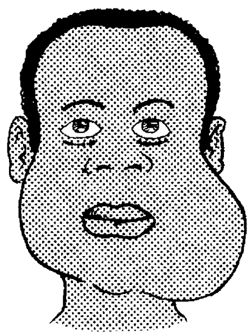
The lymphoma is slowly progressive but often eventually fatal. Sometimes it transforms into a diffuse large 'B' cell lymphoma (DLBCL).



BURKITT'S LYMPHOMA

This is a high grade lymphoma found mainly in Equatorial Africa, New Guinea and other malaria endemic areas. Similar tumours are seen in AIDS patients. The relationship with Epstein–Barr virus has already been discussed (p.81) – as has the translocation t (8;14) which activates the c-myc oncogene (p.152). The histological appearance is typical.





Endemic (African type) Burkitt's lymphoma typically presents with lesions in the jaw, or in the abdomen, e.g. ovary, liver, gastrointestinal tract. The less common cases in the West typically involve lymph node, marrow and gut.
The disease may respond dramatically to aggressive treatment.

DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL)

This is the commonest type of lymphoma and may arise in nodes or extra-nodal sites. They rapidly disseminate. They are composed of sheets of large round cells. About 50% of patients survive.

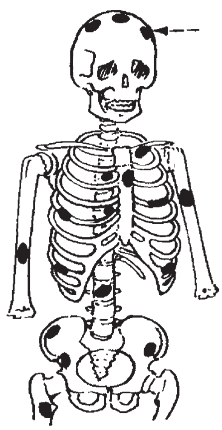
PLASMA CELL TUMOURS

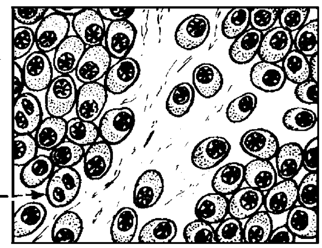
SOLITARY PLASMACYTOMA

A very small number of plasma cell tumours are solitary at presentation, e.g. in a long bone, the nasopharynx, a lymph node, alimentary tract. In 50% of cases, multiple myeloma occurs within 10 years.

MULTIPLE MYELOMA (MYELOMATOSIS)

The great majority of plasma cell tumours present as widespread deposits in the bone marrow. Classically the lesions are seen as punched out defects in the bones – the skull showing this appearance particularly well. These focal proliferations of plasma cells usually occur against a background of more diffuse infiltration throughout the marrow.



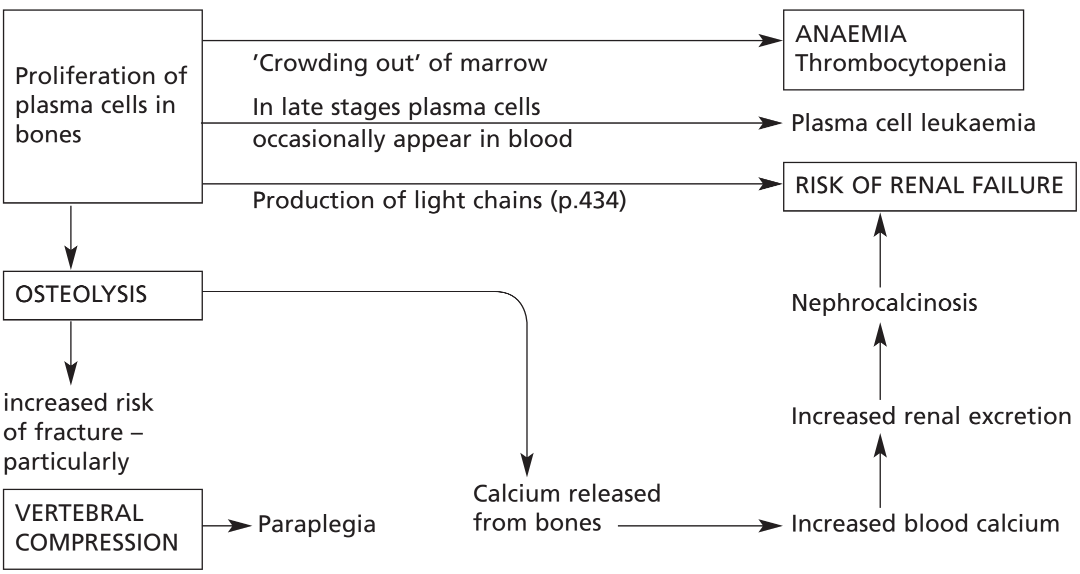


The disease has an incidence of 10/100 000 per annum with an age peak in the 7th decade.

The median survival, even with treatment, is 3 years.

Pathological effects are considered under two main headings:

1. **Tumour growth and its effects**



PLASMA CELL TUMOURS

Pathological effects (*continued*)

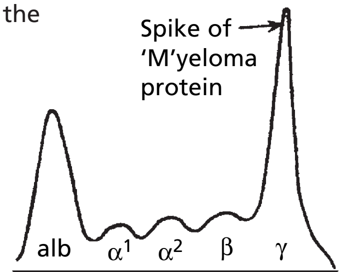
2. **Synthesis of immunoglobulin and its effects**

Myeloma, being a monoclonal tumour, will produce a single Ig. The common heavy chains are G (60%) and A (20%). In Waldenström's macroglobulinaemia the immunoglobulin is always IgM.

Light chains of κ type are encountered more frequently than λ.

The presence of a single type of Ig is reflected in the electrophoretic pattern

The other normal immunoglobulins are always decreased.



In most cases high levels of 'M' protein cause:
1. High ESR
2. Marked rouleaux formation
3. Depending on type of Ig – increased blood viscosity.

Release of light chains
In many myelomas, some of the Ig molecules are incompletely formed, and unattached light chains are released with important effects. Because of their low molecular weight the light chains:

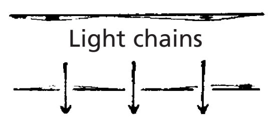
(1) Pass through the glomerular filtrate,
(a) appearing in the *urine* as Bence Jones protein (precipitates during heating – redissolves between 90°–100°C).
(b) During passage through the tubules the protein precipitates as casts and also damages the epithelial cells.



Myeloma kidney

Note giant cells

(2) Pass through capillaries



These are incorporated in AMYLOID.

↓

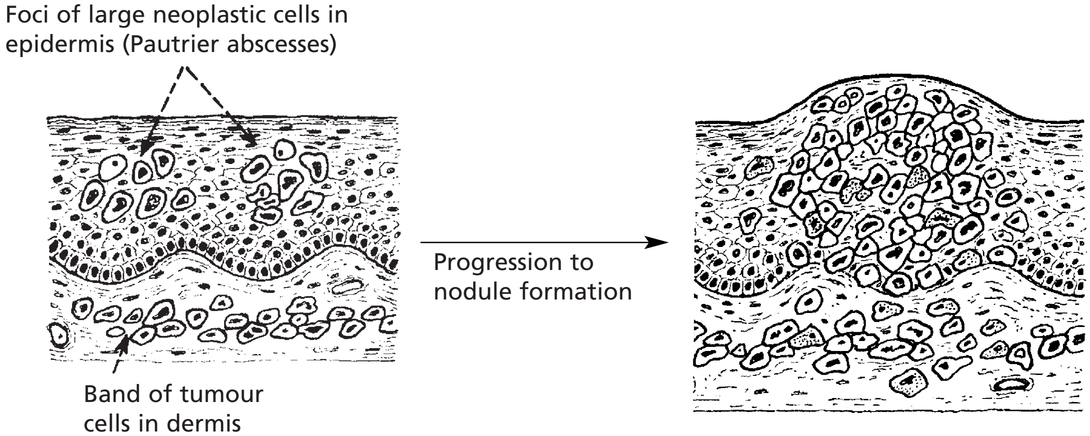
Damage to many organs, including kidneys, heart

Infections, often of opportunistic type, and particularly pneumonias are common because the immune response is deficient since the high levels of 'M' protein are non-functioning.

NON-HODGKIN'S LYMPHOMA – T CELL

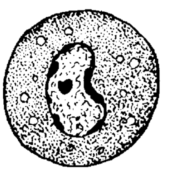
MYCOSIS FUNGOIDES

This is a primary T cell (CD4) lymphoma of the skin occurring usually in middle age. It presents as a scaly, red macule progressing to skin plaques and then nodules.



After many years the lymphoma may become generalised or exfoliate into the blood (Sézary syndrome).

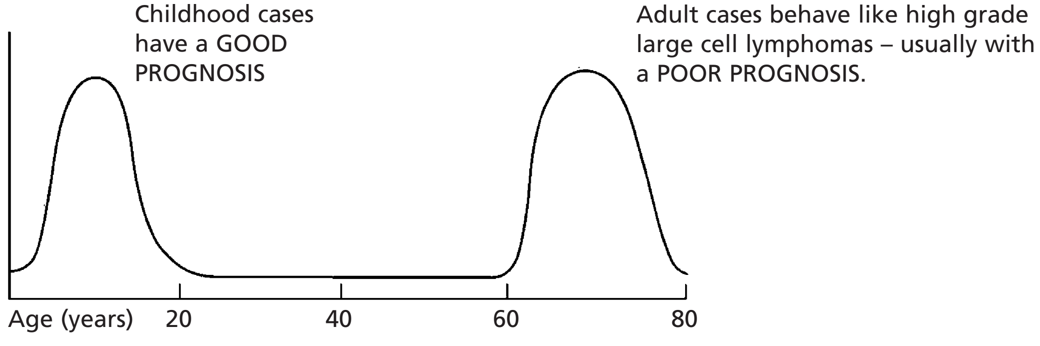
ANAPLASTIC LARGE CELL LYMPHOMA



The large malignant T cells (usually expressing surface marker CD30) often spread within the sinuses of the node and may mimic the cells in Hodgkin's disease.

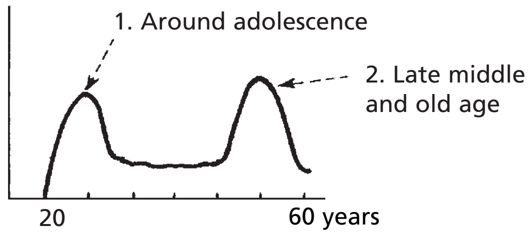
Although three-quarters of cases are of T cell type, the remainder are 'null' cell type, i.e. they express neither T nor B cell markers, causing further diagnostic difficulties. The cells express ALK-1 which resolves these difficulties.

The tumour shows 2 age peaks.



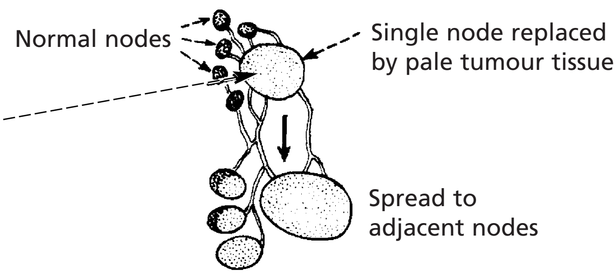
HODGKIN'S DISEASE

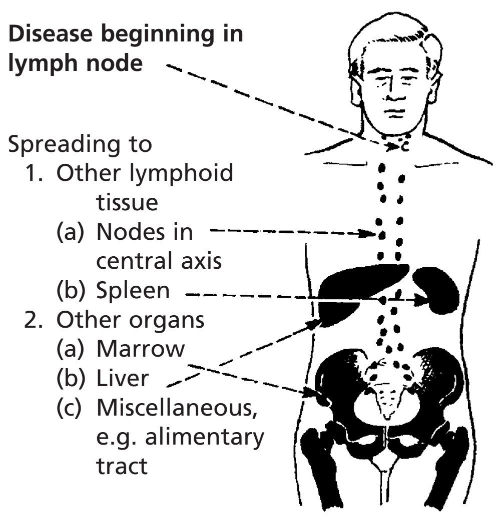
Incidence
This disease accounts for 20% of lymphomas. It may occur at any age but there are 2 peaks of incidence.



Presentation
Most patients present with painless enlargement of one or more lymph node groups – cervical, axillary, mediastinal. One quarter complain of systemic 'B' symptoms (see Staging) – fever, night sweats, weight loss, itch. The risk of infections is increased by immunosuppression.

Spread and Staging
The disease spreads from one group to the next directly connected by lymphatics.





Staging (Ann Arbor system)

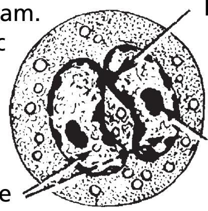
Stage I	Disease involving single node or group of nodes
Stage II	Disease in more than one site – all lesions either below or above the diaphragm
Stage III	Disease on both sides of diaphragm
Stage IV	Widespread involvement of extralymphoid sites ± lymph node involvement

The suffix (E) to the numeral indicates Extranodal disease, (A) denotes absence of systemic symptoms, (B) presence of these (see above).

HODGKIN'S DISEASE

Hodgkin's disease is diagnosed on the basis of distinctive large tumour cells known as Reed–Sternberg cells, which are now known to be 'B' cells of germinal centre origin.

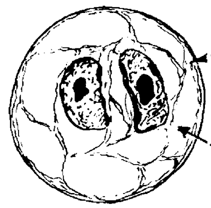
Typical RS cell



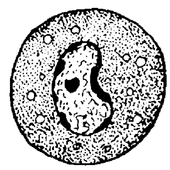
They express CD30 and CD15

Variants of RS cell

1. **The lacunar cell**



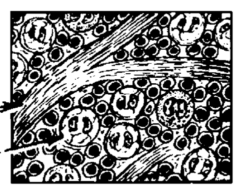
2. **Mononuclear Hodgkin's cell**



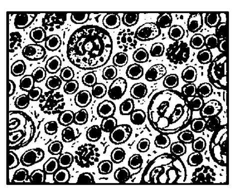
There are two main types of Hodgkin's disease:

(a) Classical HD, probably caused by EBV. There are three main forms:

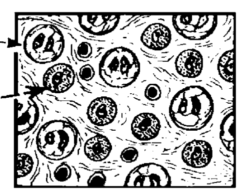
1. Nodular sclerosing (70%)



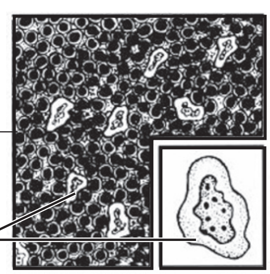
2. Mixed cellularity (20%)



3. Lymphocyte depleted (<2%)

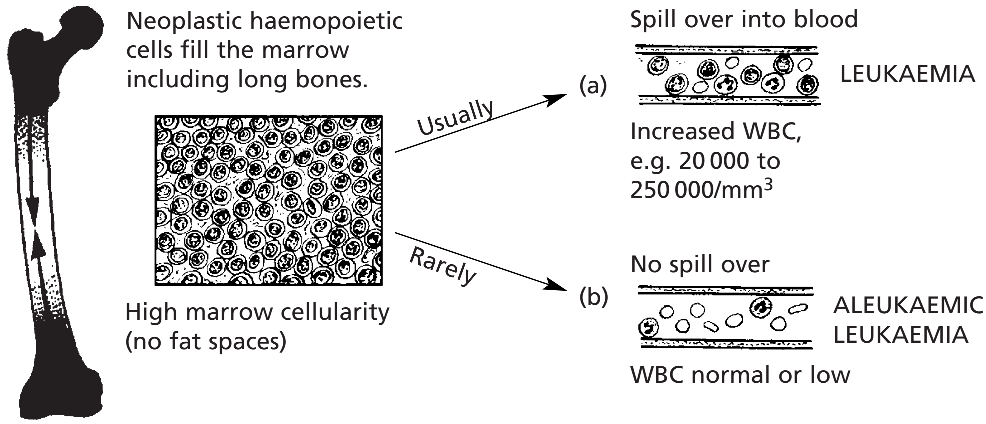


(b) Nodular lymphocyte predominant Hodgkin's disease (6%) This form affects young males and has a good prognosis. The 'popcorn cells' express 'B' cell markers and not CD30 of classic Hodgkin's disease – it is an unusual 'B' cell lymphoma.



LEUKAEMIAS

Leukaemias are primary malignant tumours of haemopoietic cells.

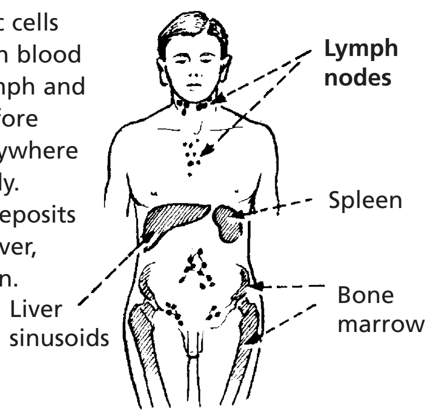


Clinical Effects
The neoplastic cells replace the normal bone marrow

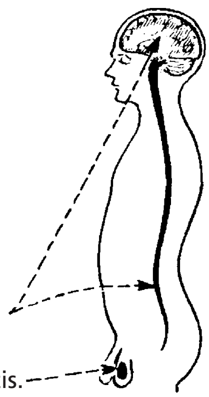
1. Deficiency of red cells ⟶ anaemia.
2. Deficiency of platelets ⟶ thrombocytopenia ⟶ bleeding.
3. Deficiency of white cells ⟶ infection.
4. Increased cell turnover ⟶ ↑DNA breakdown ⟶ ↑uric acid ⟶ gout.

Spread of leukaemia

Leukaemic cells circulate in blood and/or lymph and can therefore spread anywhere in the body. Nodular deposits are, however, uncommon.



Note: after initially successful treatment, leukaemia infiltration may recur especially in the CNS (meninges) and the testis.



LEUKAEMIAS

Classification

Leukaemias are classified according to the rate of progression and the lineage of the tumour cells. The 4 main forms are:

	MYELOID (granulocyte: monocyte series)	LYMPHOID (B and T lymphocyte series)
ACUTE LEUKAEMIA – Rapid progression – Numerous primitive 'blast' cells.	(i) ACUTE MYELOBLASTIC LEUKAEMIA	(iii) ACUTE LYMPHOBLASTIC LEUKAEMIA
CHRONIC LEUKAEMIA – Slow progression – Cells almost mature.	(ii) CHRONIC MYELOID LEUKAEMIA	(iv) CHRONIC LYMPHOCYTIC LEUKAEMIA

Rare leukaemias affect red cells, megakaryocytes and plasma cells.

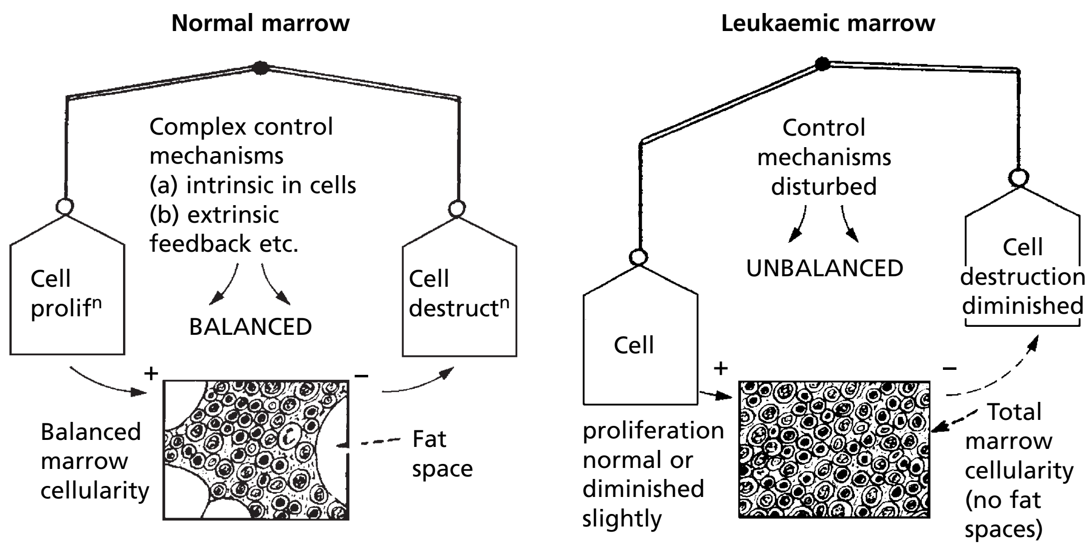
Aetiology

In most cases, the cause is unknown. Risk factors include:

1. Radiation, e.g. post Hiroshima, Chernobyl, therapeutic X-rays.
2. Chemicals, e.g. chemotherapy, benzene.
3. Genetic, e.g. Down's syndrome.
4. Virus, e.g. Human T-cell Leukaemia Virus-1.

CELL KINETICS

Even in acute leukaemias, increased cell longevity beyond the normal (due to failure of response to mechanisms controlling ageing and destruction) is as important as proliferative rates in increasing the marrow cell population.



ACUTE MYELOBLASTIC LEUKAEMIA

This is the commonest acute leukaemia of adults – 80% of patients are over 60 years old. Young adults and children may also be affected.

It may arise de novo or in association with chronic myeloid leukaemia, myeloproliferative disorders, myelodysplasia. The onset and progression to marrow failure is rapid, clinically presenting as anaemia, haemorrhage or serious infection.

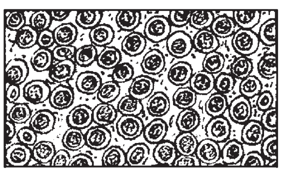
The WHO classification describes four broad categories:

1. AML with recurrent genetic abnormalities. The differing genetic rearrangements have major implications for prognosis and treatment.
2. AML with multilineage dysplasia – usually following myelodysplastic syndrome.
3. AML, therapy related – usually after alkylating chemotherapy.
4. AML, not otherwise classified – a wide variety showing varying degrees of differentiation, e.g. acute monocytic, acute erythroblastic, acute myelomonocytic.

PATHOLOGY

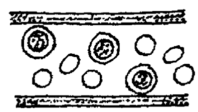
The marrow

Over-run by blast cells



The blood

Decreased platelet count – **thrombocytopenia.**

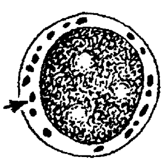


2/3 cases: WBC 20 000–50 000 blast cells
1/3 cases: **aleukaemic**

Other organs may be involved: Splenomegaly, hepatomegaly and lymph node enlargement. More specific pathological clinical complications are seen in 2 subtypes.

Promyelocytic

Primitive cell with primary myeloid granules



A typical chromosomal translocation t(15:17) is found.

Patients often develop disseminated intravascular coagulation.

Myelomonocytic and Monocytic



Infiltration of the gums and central nervous sytem is often seen.

CHRONIC MYELOID LEUKAEMIA (CML)

This form of leukaemia arises from malignant transformation of a primitive stem cell – but with the production of differentiated cells – particularly neutrophils.

This is a disease of middle age. There are 3 phases:

1. **Chronic phase** – a period of slow evolution – 2–6 years is typical.
2. **Accelerated phase** – an increase in immature cells.
3. **Blast phase** – transformation to an acute leukaemia – myeloblastic or, very rarely, lymphoblastic.

Rarely patients develop myelofibrosis with marrow failure.

Marrow



Total cellularity: cells of granulocyte series – late forms numerous (including eosinophil and basophil types). Often increase in megakaryocytes; may be increased fibrosis. Increased pressure in bones may cause tenderness and pain.

Blood

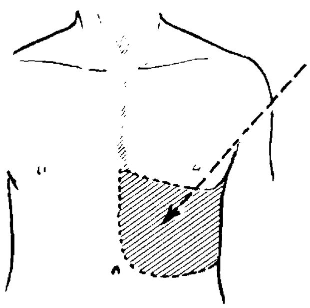
(a) WBC: 75 000–250 000/mm^3
Differential WBC
Blasts } <5%
Promyelocytes }

Majority of cells are late myelocytes and mature granulocytes

(b) ANAEMIA

(c) THROMBOCYTOPENIA
(sometimes thrombocytosis)

Splenomegaly



Firm, may be massive, e.g. 3 kg

May be infarction
↓
Clinically painful



Lymphoid follicles inconspicuous

Red pulp with cells of granulocyte series
± megakaryocytes
± red cell precursors

Philadelphia (Ph) chromosome
In over 95% of cases of CML there is a specific cytogenetic change t(9;22)(q34;q11) with the formation of the 'Ph chromosome'.

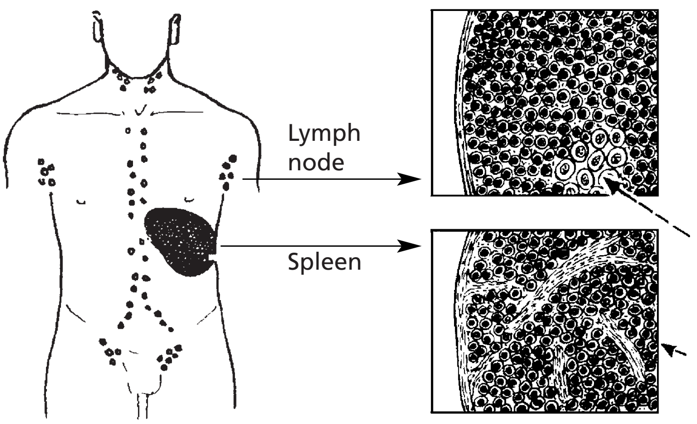
The change involves a translocation of the c-abl gene (an oncogene) from chromosome 9 to chromosome 22 where hybridisation with the bcr gene occurs. A tyrosine kinase inhibitor (IMATINIB) which targets this pathway has been introduced.

CHRONIC LYMPHOCYTIC LEUKAEMIA

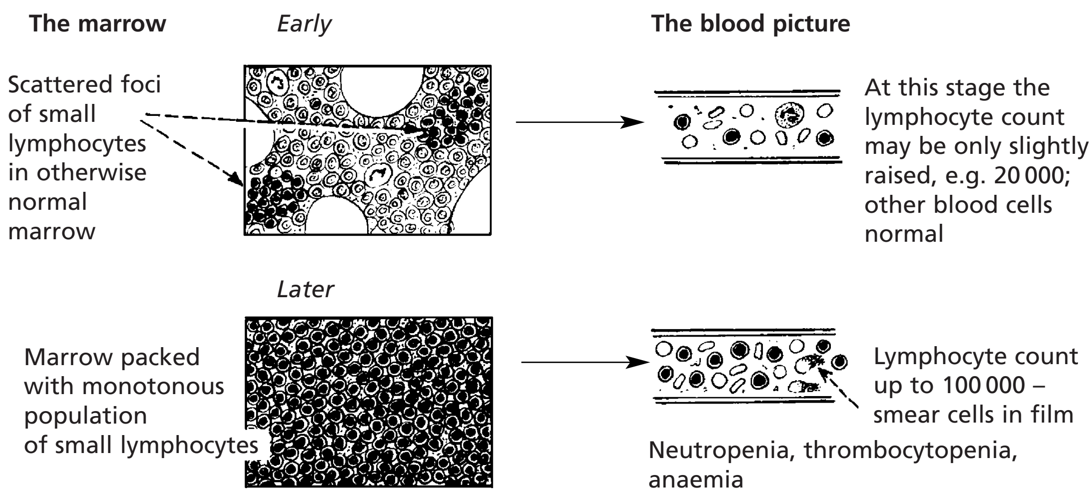
This is a common form of leukaemia (25% of all cases) and particularly affects middle aged and elderly patients. It is a monoclonal proliferation of small lymphocytes and is best regarded as the leukaemic form of lymphocytic lymphoma.

Most cases are of B cell type – less than 5% are of T cell lineage.

There is typically lymph node enlargement and splenomegaly.



In some cases the lymphoid enlargement precedes the leukaemic phase.



In addition to anaemia these patients often suffer recurrent infections due to defective immunity.

In a minority of cases (approximately 5%) transformation to a high grade ‘B’ cell lymphoma results (Richter syndrome).

ACUTE LYMPHOBLASTIC LEUKAEMIA (ALL)

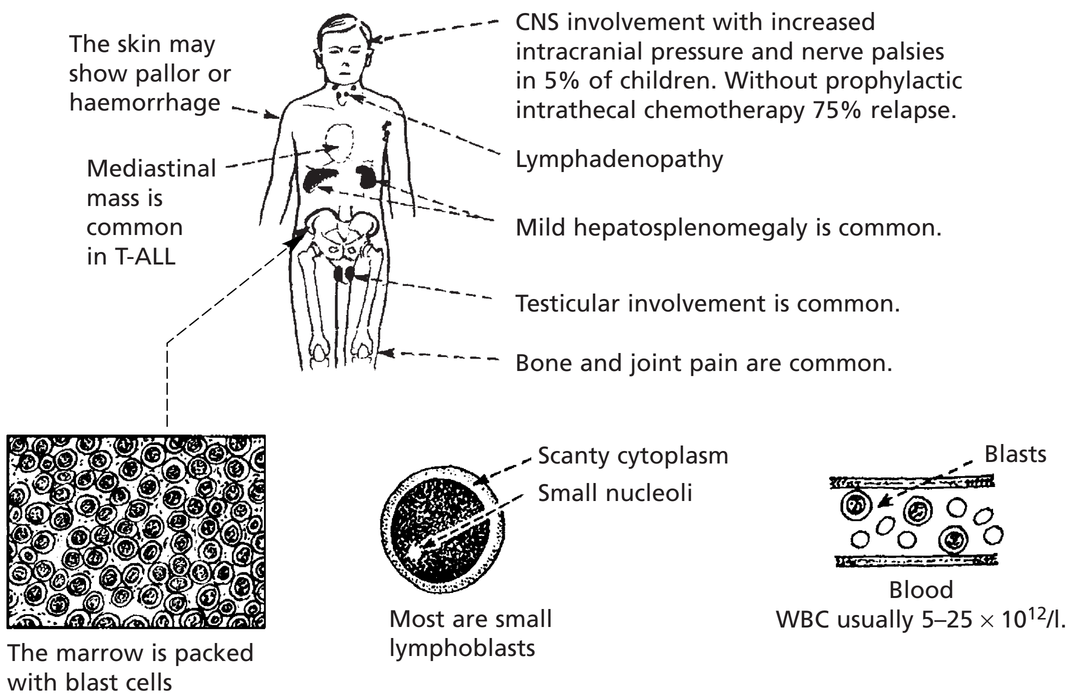
This term describes a group of leukaemias of lymphocytic precursors. ALL is the commonest form of childhood leukaemia but is also seen in adults.

Like AML, immunological and genotypic classification is increasingly important. Broadly, they are classified as follows:

- Precursor B cell > 80%
- Precursor T cell 15%
- Null cell.

ALL in Childhood

This is usually of Precursor B ALL type



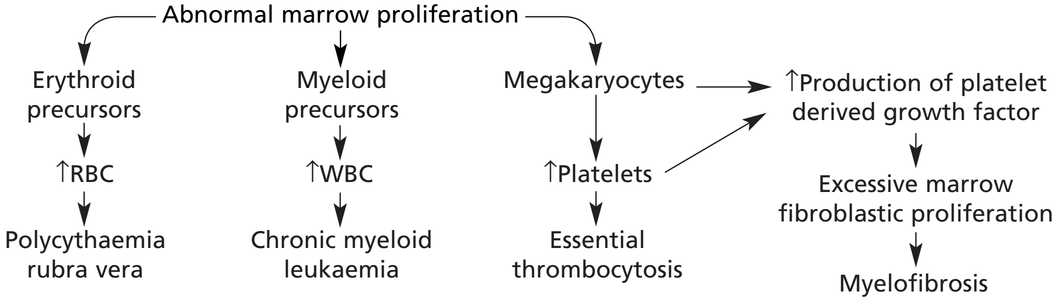
Childhood ALL is now potentially curable – 70% survive 5 years.

ALL in Adults

Adults have a worse prognosis and often require bone marrow transplantation as well as chemotherapy.

MYELOPROLIFERATIVE DISORDERS

In this group of diseases, neoplastic transformation of a haemopoietic precursor cell may lead to excess production of erythrocyte, leucocyte or platelet precursors. In many cases more than one element is affected. Transformation to acute leukaemia can occur in all forms. This can be summarised as follows:

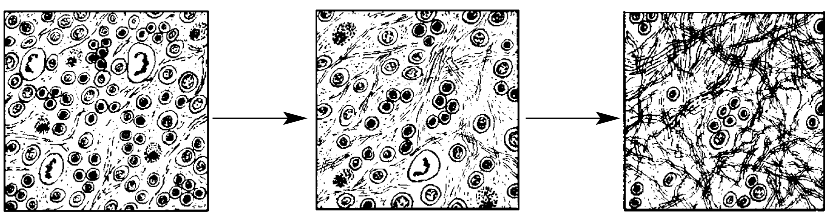


In these conditions excess marrow proliferation may be seen in liver, spleen and other organs – EXTRAMEDULLARY HAEMOPOIESIS (EHM).

MYELOFIBROSIS

When haemopoietic cellular proliferation is overshadowed by progressive FIBROSIS of the marrow, SPLENOMEGALY (often of massive proportions) due to EXTRAMEDULLARY HAEMOPOIESIS is often found.

Marrow: ordinary marrow puncture usually results in a 'dry tap', therefore trephine or cutting needle biopsy is required



Total cellularity – all types of cell – very early reticulin increase.

Reticulin ++ – early fibrosis – cellularity decreasing.

Established fibrosis – only small foci of haemopoietic cells remaining.

At this stage bone changes may be seen on X-ray – OSTEOSCLEROSIS.

Blood findings

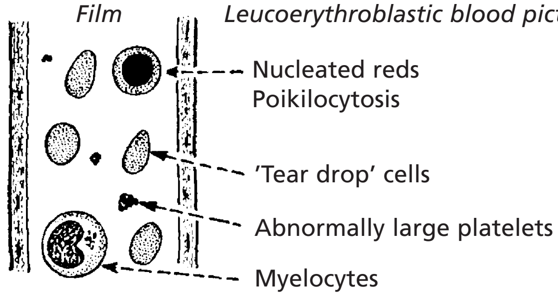
RBC	WBC	Platelets
low	may be increased	may be increased

as marrow cells are replaced

↓

Progress to PANCYTOPENIA (this is exaggerated by enlarged spleen)

Film *Leucoerythroblastic blood picture*



2. MYELODYSPLASTIC SYNDROMES (MDS)

These are primary disorders of stem cells associated with several different chromosomal abnormalities. They lead to ineffective haemopoiesis of varying types, with the appearance in the peripheral blood of abnormal cells. A significant number progress to LEUKAEMIA.

CHAPTER 12

GENITOURINARY SYSTEM

KIDNEY – STRUCTURE AND FUNCTION

The kidney has several functions:

1. Eliminating waste products.
2. Controlling electrolyte and fluid balance.
3. Contributing to acid–base balance.

} By filtering plasma and modifying the filtrate to produce urine.

It produces several hormones:

(i) *Renin*, which influences vascular tone and blood pressure.
(ii) *Erythropoietin*, which increases red blood cell production.
(iii) *1, 25 dihydroxy Vitamin D* – The active form is produced by 1α hydroxylation in the kidney. It promotes calcium absorption from the gut and is required for normal bone mineralisation.

Tests of renal function:

1. **Blood analysis**

Many substances will show altered values in renal failure, but the following are always elevated and are commonly used in estimating the progress of the disease.

(i) Urea – normal range 2.5–7.0 mmol/l. (20–40 mg/100 ml)

(ii) Creatinine – 50–100 mmol/l. (0.6–1.2 mg/100 ml)

2. **Clearance Tests** (typically creatinine clearance) give an indication of glomerular filtration rate: this is not absolute since some creatinine is secreted by renal tubules. The following formula is used to calculate the volume of blood cleared:

Clearance = $\frac{UV}{P}$ where:

U = urinary concentration,
V = volume of urine per minute,
P = plasma concentration.

In practice renal function is now commonly assessed by estimated glomerular filtration rate (eGFR), which combines serum creatinine with the age and sex of patient.

Chronic Kidney Disease can be classified as follows:

CKD	Stage	eGFR/mL/min/1.73m^2
1	with an abnormality*	>90
2	with an abnormality*	60–89
3		30–59
4		15–29
5		<15

*e.g. proteinuria

3. **Urine examination**

(a) Tests for the presence of protein, red cells, haemoglobin and neutrophils in the urine. Estimation of specific gravity and measurement of urinary output.
(b) Urinary casts. These are composed of foreign elements of various types which are moulded into cylindrical form by passage along tubules and are seen on microscopy.
(c) Culture

The Kidney is divided into:

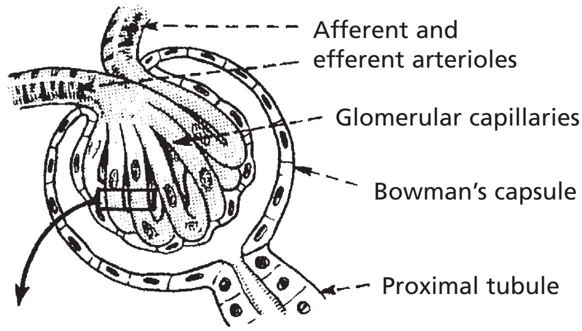
(a) glomeruli
(b) tubules
(c) interstitium
(d) vessels.

The structure and function and diseases will be discussed separately, but diseases of one may well affect others.

GLOMERULAR STRUCTURE AND FUNCTION

The glomerulus, of which there are over 600 000 in the adult, consists of an invagination of a capillary network, derived from the afferent arteriole, into Bowman's capsule – the beginning of the proximal tubule.

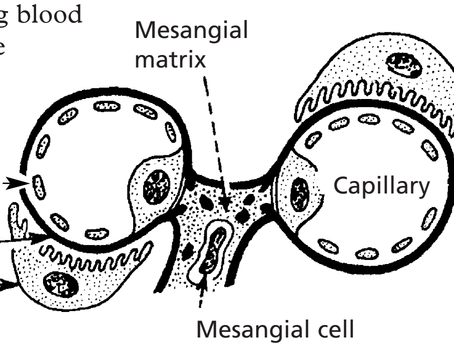
The glomerulus is an efficient filter due to the large surface area of the glomerular capillaries.



Ultrastructure

The barrier separating blood from the lumen of the nephron consists of 3 layers:

1. Endothelium (fenestrated)
2. Basement membrane
3. Epithelium

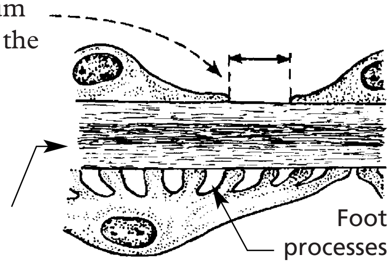


Mesangial cells have three functions:

1. Contract and control blood flow
2. They are phagocytic cells and ingest proteins and immune complexes (p.101)
3. They form matrix and secrete inflammatory mediators.

These layers form a complicated sieve controlling glomerular permeability. Wide pores (70–100 nm) in the endothelium allow all components to reach the basement membrane.

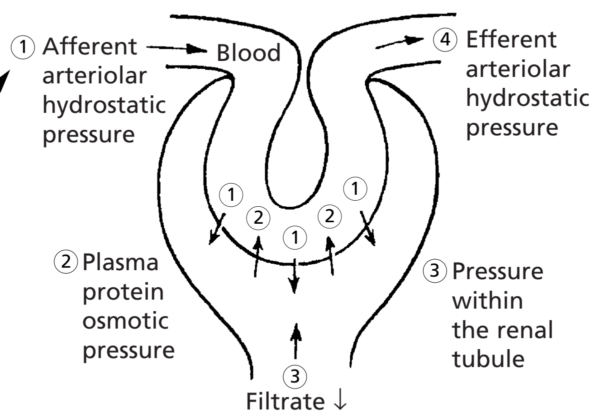
The basement membrane produced by the endothelium and epithelium has a strong anionic (negative) charge which repels major plasma proteins (also anionic). It has a central dense layer (lamina densa).



The epithelial cells are attached to the basement membrane by foot processes, separated by 'slit pores' 30–60 nm in diameter.

Filtration

The glomerular filtrate is virtually protein free plasma. Its rate of production is dependent upon:



Variation in any of these factors affects the output of urine. Diminished urinary output results from a reduction in renal blood flow as in shock, from an increase in osmotic pressure as in haemoconcentration, or from obstruction to the outflow of urine.

GLOMERULAR DISEASES

Glomerular damage results in:
1. Reduction in urinary output.
2. Proteinuria.
3. Haematuria.

The mechanisms underlying these changes are as follows:

Swelling of endothelium → Diminished blood flow → Reduction in urine

Inflammation altering permeability of layers → Proteinuria

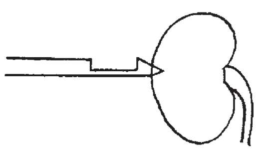
Focal loss of epithelium and endothelium → Proteinuria; → Haematuria

These lead to 4 main clinical syndromes:

1. The NEPHRITIC SYNDROME – characterised by moderate proteinuria, haematuria, oedema, oliguria and often renal impairment. Hypertension is common.
2. The NEPHROTIC SYNDROME
   Heavy proteinuria (>3.5 g/day) ⟶ Hypoalbuminaemia ⟶ Oedema
3. RENAL FAILURE – acute or chronic in type
4. Asymptomatic haematuria or proteinuria.

The main causes are:
(a) IMMUNE DAMAGE ⟶ GLOMERULONEPHRITIS
(b) DIABETES MELLITUS
(c) Vascular disease, e.g. hypertension.

The cause is best determined by renal biopsy.



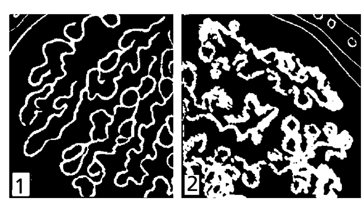


The core of tissue obtained is examined by:

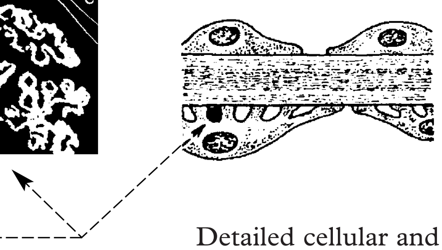
1. **Light microscopy**



2. **Immunofluorescence**



3. **Electron microscopy**



Shows
1. Increase in cells,
2. Details of basement membrane and
3. Mesangial matrix.

Immune complexes can be detected.
1. Linear
2. Granular

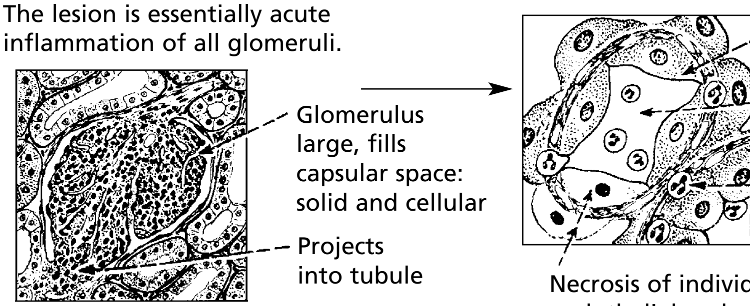
Detailed cellular and membrane damage can be seen.

 The main forms of glomerular disease are described in the following pages.

ACUTE DIFFUSE PROLIFERATIVE GLOMERULONEPHRITIS

This disease classically follows 2–3 weeks after an infection – usually pharyngitis due to Group A haemolytic streptococci. It is commonest in children and young adults who develop the NEPHRITIC SYNDROME: oliguria, proteinuria, haematuria (urine is smoky and dark), moderate hypertension and facial (periorbital) oedema. This disease is now uncommon in fully developed countries.

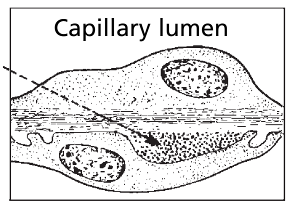
The lesion is essentially acute inflammation of all glomeruli.



Immune complexes are identified by:

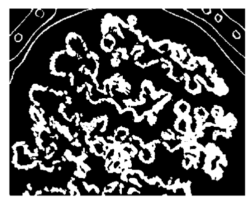
1. **Electron microscopy**

Hump-shaped electron-dense granular deposits seen in subepithelial position



and 2. **Immunofluorescence**

– demonstrates granular deposition of IgG and C3 (complement component 3)



The clinical findings can be correlated with pathology as follows:

Glomerular capillary obstruction → Reduced blood flow

Reduced blood flow → Tubular epithelial damage

Reduced blood flow → Stimulation of juxtaglomerular apparatus → **Rise in blood pressure**

Reduced blood flow → Diminished filtration → Oliguria → **Raised blood urea**

Diminished filtration → Fluid retention → **Oedema**

Tubular epithelial damage → Fluid retention

Tubular epithelial damage → Casts

Oliguria → **Oedema**

Damaged glomerular endothelium → Focal increase in permeability → **Unselective proteinuria** → **Oedema**; → Casts

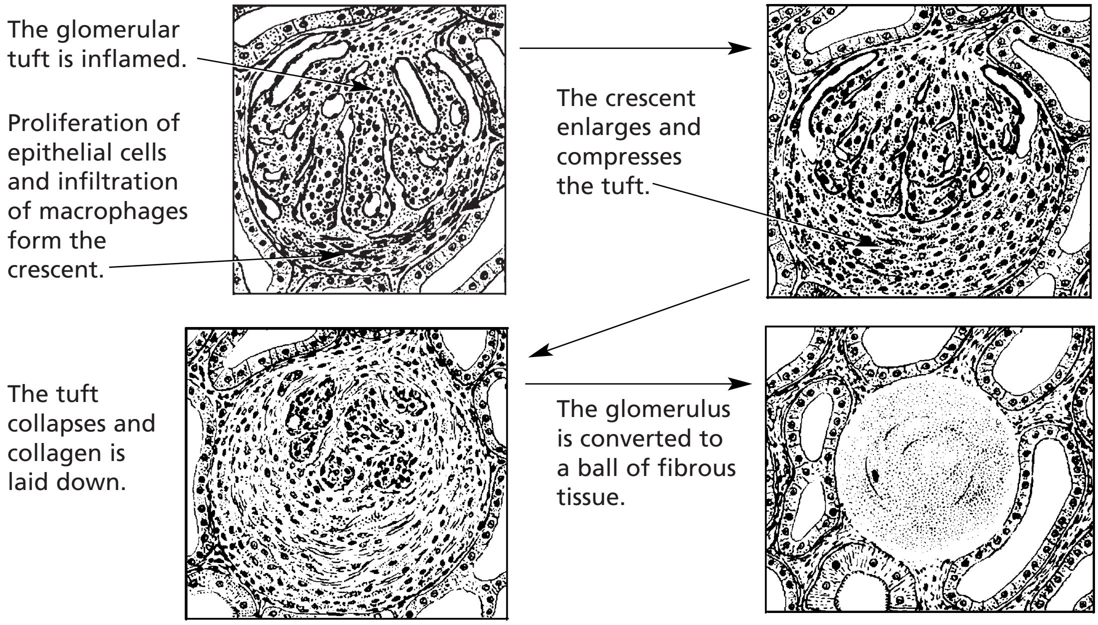
Damaged glomerular endothelium → Escape of red cells → **Haematuria** → Casts

Prognosis – The disease usually resolves in 1–2 weeks, particularly in children, but in adults complications are more common.

1. Mild proteinuria persisting for a month or two → RECOVERY
2. Rapidly progressive glomerulonephritis (rare) → Poor prognosis
3. Cardiac failure or uraemia → DEATH in acute phase **(very rare)**
4. Persisting proteinuria and haematuria → CHRONIC NEPHRITIS → DEATH years later

CRESCENTIC (RAPIDLY PROGRESSIVE) GLOMERULONEPHRITIS

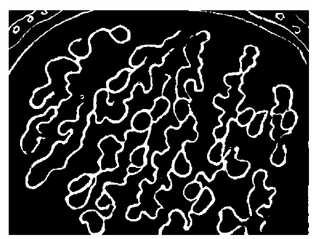
Without treatment, this disease progresses to end-stage renal failure in weeks or months. The histological hallmark is **crescent formation** in >50% of glomeruli.



Many types of glomerulonephritis can progress to crescentic GN. Examples include:

1. **Goodpasture's syndrome**
   In this serious disorder there is both renal and often pulmonary damage. Immunofluorescence shows the cause – an antibody to type IV collagen in the glomerular basement membrane (anti-GBM) which also damages pulmonary alveolar membranes.

IF shows linear deposits of IgG and C3 in the capillary basement membranes



Anti-GBM antibody → Renal damage (crescentic GN) / Lung damage (haemorrhage) } Renal and/or pulmonary failure

RPGN may complicate:

2. **Vasculitis** – e.g. Wegener's granulomatosis, microscopic polyarteritis nodosa.
3. **Systemic Lupus Erythematosus.**
4. **Acute diffuse proliferative glomerulonephritis,** especially in adults.
5. **IgA nephropathy.**

Prognosis – Without treatment, most patients die within 6 months. Immunosuppressive drugs (e.g. steroids, cyclophosphamide) and plasma exchange to (remove anti-GBM antibodies) improve the prognosis but many patients require dialysis or transplantation. Hypertension is a further serious complication.

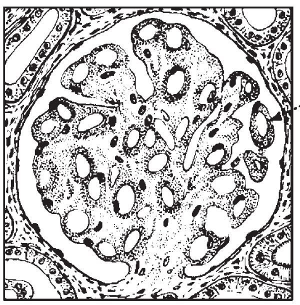
MEMBRANOUS GLOMERULONEPHRITIS

This accounts for around 30% of cases of the nephrotic syndrome in adults; some patients present with asymptomatic proteinuria.

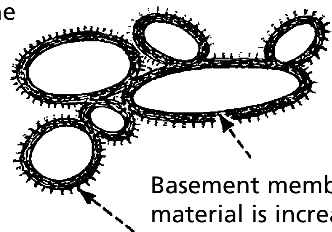
Aetiology

1. Around 85% of cases are IDIOPATHIC.
2. Drugs, e.g. penicillamine – in treatment of rheumatoid arthritis.
3. Tumours, e.g. carcinoma of lung, lymphomas.
4. Infections, e.g. malaria, HIV, hepatitis B, syphylis.
5. Collagen disorders, e.g. SLE.

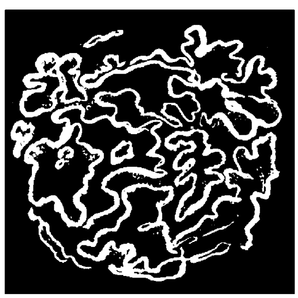
Pathology – There is generalised thickening of capillary basement membrane.



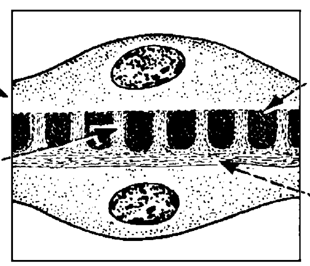
Specific silver staining of the basement membrane shows a typical pattern.



Immunofluorescence reveals deposition of IgG in the capillary walls.

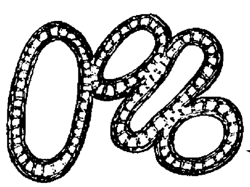


Electron microscope findings explain this appearance.

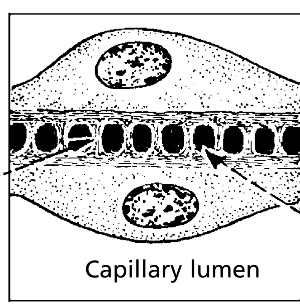


In the later stages there is a massive increase in basement membrane material.

Silver staining shows



Electron microscope shows

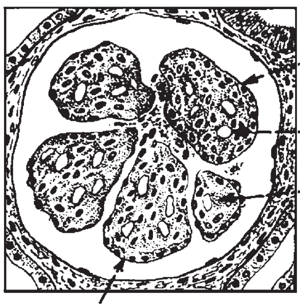


Tubular changes – In the early stages, protein droplets and lipid globules appear in the tubular epithelium. If the disease progresses there is atrophy of the tubules and interstitial fibrosis.

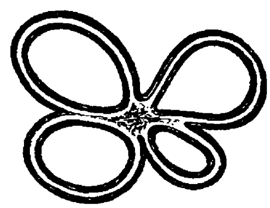
Prognosis – In about 25% of patients the disease remits spontaneously, the remainder continuing to have proteinuria and in 40% chronic renal failure eventually supervenes.

MESANGIOCAPILLARY (MEMBRANOPROLIFERATIVE) GLOMERULONEPHRITIS

In this form of glomerulonephritis there is an increase both in **cells** and **mesangial matrix** within glomeruli.

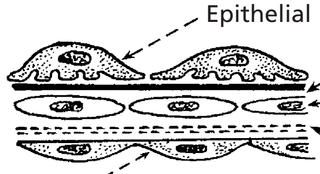


Silver staining of basement membrane

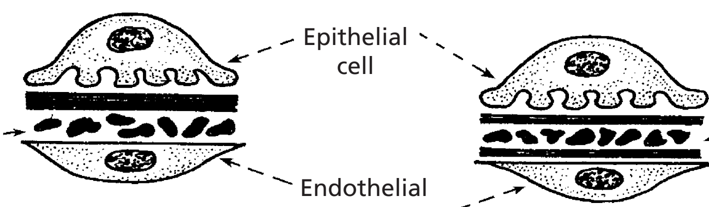


Duplication of basement membrane as in membranous glomerulonephritis, but without spikes.

These changes are due to **'mesangial interposition'**



Using electron microscopy and immunofluorescence, 2 types are identified.



Aetiology

Complement activation is a feature of both forms. In Type 1 this is due to immune complexes by the classical pathway (p.99). In Type 2 there is activation by the alternative pathway by an autoantibody which stabilises C3 converting enzyme. Serum C3 is low in both forms.

Clinical features

Children and young adults are usually affected. They present with the **nephrotic syndrome** (50%), the nephritic syndrome or asymptomatic haematuria or proteinuria.

In half of patients there is progression to renal failure (with hypertension) within a decade. The disease often recurs in the subsequently transplanted kidney.

FOCAL GLOMERULONEPHRITIS

In contrast to the glomerular diseases discussed already, focal glomerulonephritis affects only a proportion of glomeruli (focal) and only part of those glomeruli (segmental).

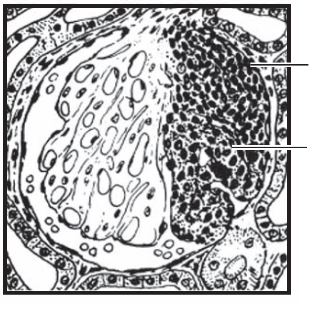


In some cases, part of the tuft becomes necrotic and there is related inflammation (focal segmental necrotising glomerulonephritis). Crescents are sometimes seen. This pattern is seen in:

- Systemic vasculitis, e.g. polyarteritis nodosa
- IgA nephropathy and Henoch–Schönlein purpura
- SLE (systemic lupus erythematosus)
- Some cases of Goodpasture's syndrome
- Infective endocarditis.

The pattern is associated with haematuria or nephrotic syndrome. Segmental lesions heal by fibrosis.

Focal Segmental Glomerulosclerosis (FSGS)
In this pattern of disease, a segment of glomerulus undergoes sclerosis without inflammation, but with an increase in mesangial matrix.



Originally regarded as a variant of minimal change nephropathy, primary FSGS presents as with haematoma or nephrotic syndrome with progression to chronic renal failure. It may recur within a transplanted kidney.

Secondary FSGS may complicate a variety of preexisting conditions including those reflux nephropathy and intravenous drug use.

IgA NEPHROPATHY

This is the commonest form of glomerulonephritis worldwide. It can present with microscopic or macroscopic haematuria or the nephrotic syndrome and may lead to chronic renal failure. It typically affects young males, who often suffer recurrent episodes after upper respiratory infections although all ages can be affected.

The serum IgA level is raised and glomerular damage is due to IgA immune complexes. Sometimes crescentic glomerulonephritis is seen.

Mechanism

IgA immune complexes in blood ⟶ Glomeruli ⟶ **Often focal deposition** ⟶ Activation of complement (C3) ⟶ **Often focal damage**

Immunofluorescence



Shows deposits of IgA and C3 within the mesangium: the capillary loops are not usually affected.

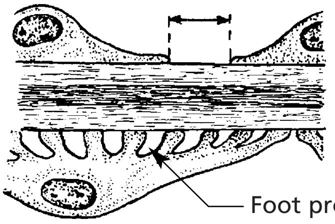
Note: The focal deposition is dependent on the molecular size of the complex and failure of mesangial clearance.

Henoch–Schönlein purpura has similar renal changes but also skin rash and gastrointestinal symptoms.

MINIMAL CHANGE GLOMERULONEPHRITIS

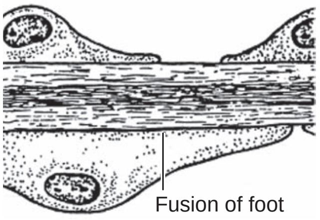
This disorder affects any age but is the major cause of nephrotic syndrome in children. It typically remits spontaneously and responds to a short course of steroids. Recurrences are quite common.

Normal



The glomeruli are histologically normal, but electron microscopy reveals fusion of podocyte foot processes. This is a finding in many causes of proteinuria. No immune complexes are found on immunofluorescence or electron microscopy.

Minimal change

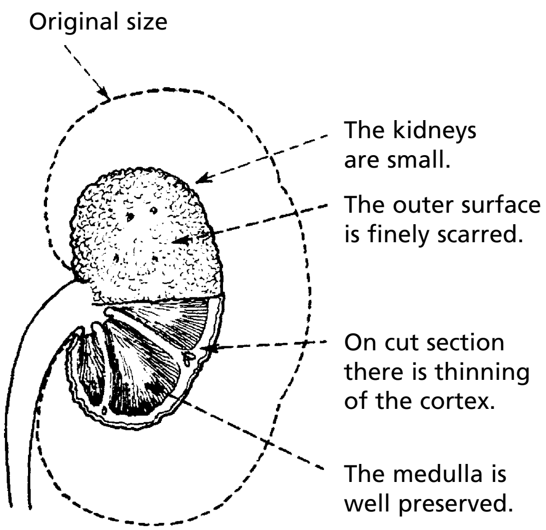


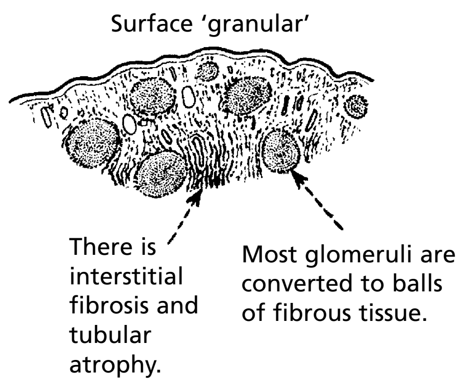
CHRONIC GLOMERULONEPHRITIS (GN)

This is the end stage of many forms of glomerulonephritis, but most patients present at this stage without a history of previous renal disease.

Rapidly progressive GN → CHRONIC GN
IgA nephropathy → CHRONIC GN
Mesangiocapillary GN → CHRONIC GN
Membranous GN → CHRONIC GN
Focal glomerulosclerosis → CHRONIC GN

Pathology The kidneys are both small – granular contracted kidney.





In chronic glomerulonephritis a vicious cycle is set up.

GLOMERULAR DAMAGE → HYPERTENSION → GLOMERULAR DAMAGE

Patients may first present with chronic renal failure, or this may develop after years of glomerulonephritis.

GLOMERULONEPHRITIS – DISEASE MECHANISMS

The mechanism in most forms of GN is:

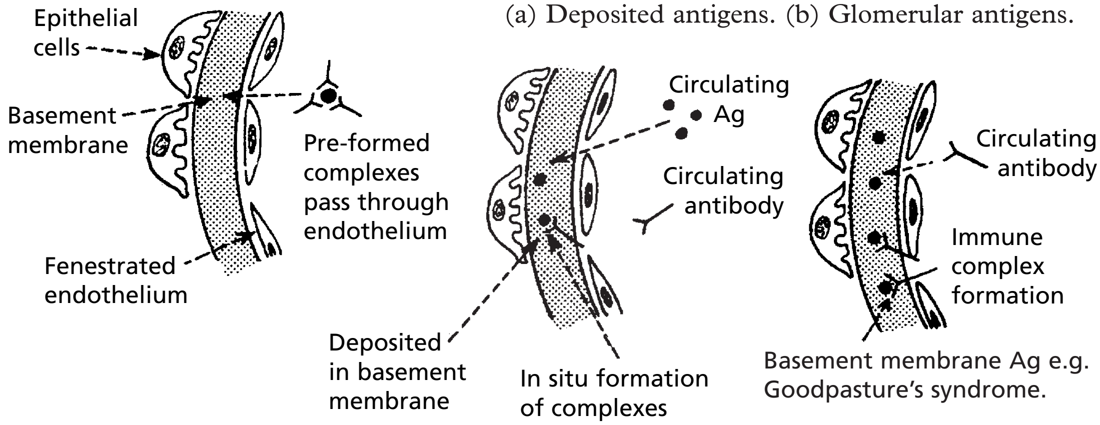
Immune complex formation → Activation of **complement** → **Cell damage** / **Neutrophil** activation → Glomerular injury

The glomerulus is central to immune complex deposition and formation due to its **fenestrated endothelium** and **high intraluminal pressure**.

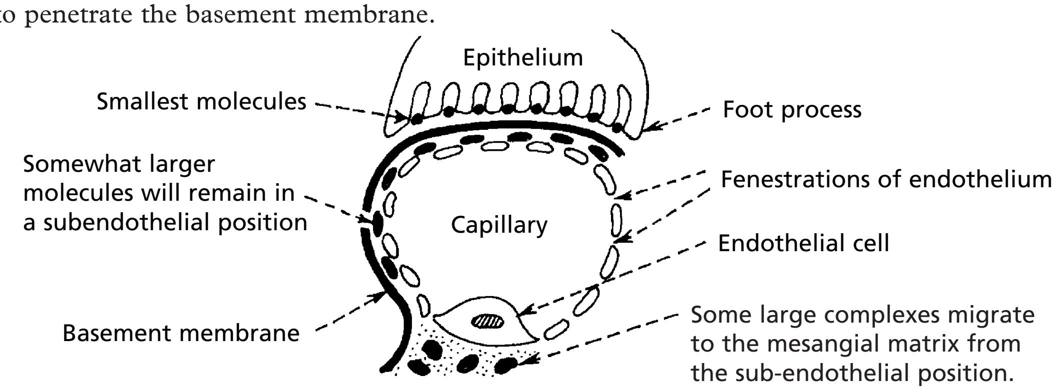
Immune complexes can occur in glomeruli as follows:

1. Deposition of circulating complex.

2. In situ formation of complexes
(a) Deposited antigens. (b) Glomerular antigens.



Localisation of complexes
This depends on the size of the complexes, their shape and electrical charge, and their ability to penetrate the basement membrane.



Other factors modifying the pathological changes are:
(i) Amount of antigen, (ii) Intensity of the immune reaction, (iii) Type of antibody (especially IgA), (iv) Availability of complement, (v) Degradation of complexes by macrophages and mesangial cells, (vi) Secondary tubular damage has important effects on renal function.

Note: In addition to its damaging consequences, complement activation does **solubilise complexes** allowing their disposal. Thus complement deficiency may predispose to immune complex disease, e.g. in systemic lupus erythematosus (SLE).

GLOMERULAR DISEASE IN SYSTEMIC DISORDERS

SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)

At least 50% of patients with SLE have clinical evidence of renal involvement, and almost all will have abnormalities on renal biopsy.

The main consequences are:
(1) Proteinuria ⟶ nephrotic syndrome.
(2) Microscopic haematuria.
(3) Hypertension.
(4) Progression to renal failure.

The renal changes form a spectrum.

Minimal abnormalities — Focal glomerulonephritis — Diffuse proliferative glomerulonephritis

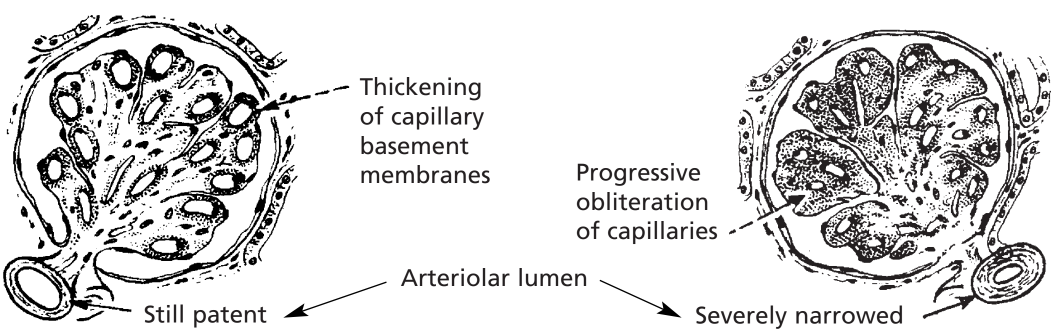
MILD ⟶ **SEVERE**

On immunofluorescence, IgG, C3 are almost always present and IgA, IgM, Clq and C4 are often also seen.

WHO classification
(i) No lesion by light microscopy
(ii) Mesangial proliferation
(iii) Focal (<50%) proliferation
(iv) Diffuse (>50%) proliferation
(v) Membranous
(vi) Chronic renal damage.

AMYLOIDOSIS

The general features of amyloidosis have already been described (p.24). Amyloid is deposited around the capillary basement membranes of the glomeruli and in the renal vessels and interstitium.



Gross proteinuria leading to a nephrotic syndrome is common. Interstitial fibrosis results from tubular degeneration and ischaemia due to glomerular and arteriolar lesions. Chronic renal failure results.

Parasitic glomerulopathies

The kidney and particularly the glomeruli are damaged in many parasitic infections in the tropics. **Malaria** and **schistosomiasis** are especially important.

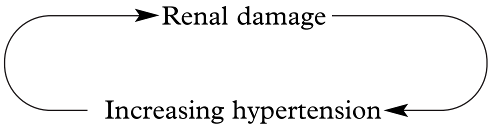
THE KIDNEY and HYPERTENSION

There are two aspects to the relationship of the kidney and high blood pressure.

(a) Many renal diseases lead to hypertension (p.197).

(b) Hypertension leads to renal damage.

A vicious circle can be set up:

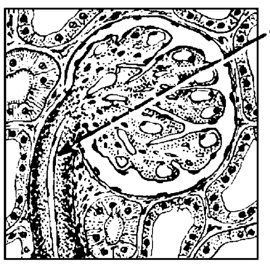


Activation of the Renin-Angiotensin system is important.

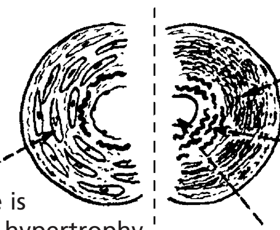
The renal consequences of benign and malignant hypertension differ, but in each, vascular changes are important.

BENIGN HYPERTENSION

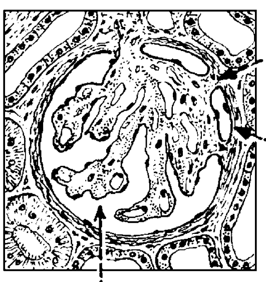
Afferent arterioles



Interlobular arteries



These arteriolar changes lead to glomerular ischaemia.



Late



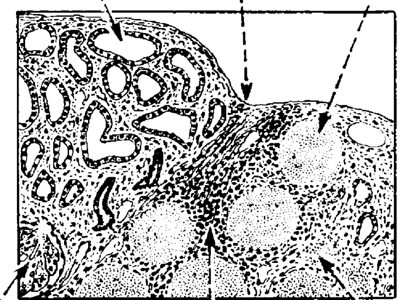
The tubules atrophy and there is interstitial fibrosis.

These changes are patchy in distribution so that renal failure rarely occurs.

THE KIDNEY AND HYPERTENSION

BENIGN HYPERTENSION (*continued*)





It is now thought that small emboli from atheroma of the aorta are responsible for much of the scarring in benign hypertension.

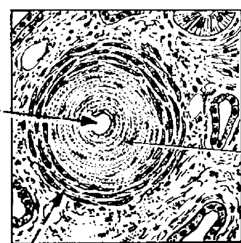
MALIGNANT HYPERTENSION

In this form of hypertension which may arise *de novo* or on a background of benign hypertension. There is often an underlying cause for the hypertension the blood pressure rises very rapidly and damages renal arteries, arterioles and glomeruli. Renal failure is common unless the disease is treated.

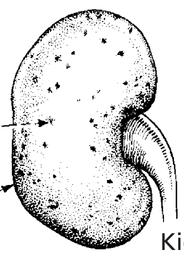
Afferent arterioles: the hallmark is **fibrinoid necrosis.**

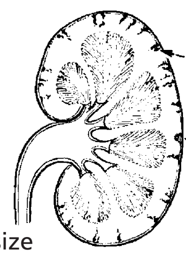


Fibrinoid necrosis heals with the production of an 'onion-skin' lesion.



These changes account for the gross appearance.





CHRONIC RENAL FAILURE

Progressive renal damage in many kidney diseases eventually leads to chronic renal failure. The major causes include:

(a) Chronic glomerulonephritis.
(b) Chronic pyelonephritis and interstitial nephritis.
(c) Diabetic nephropathy.
(d) Obstructive uropathy.
(e) Polycystic kidneys.

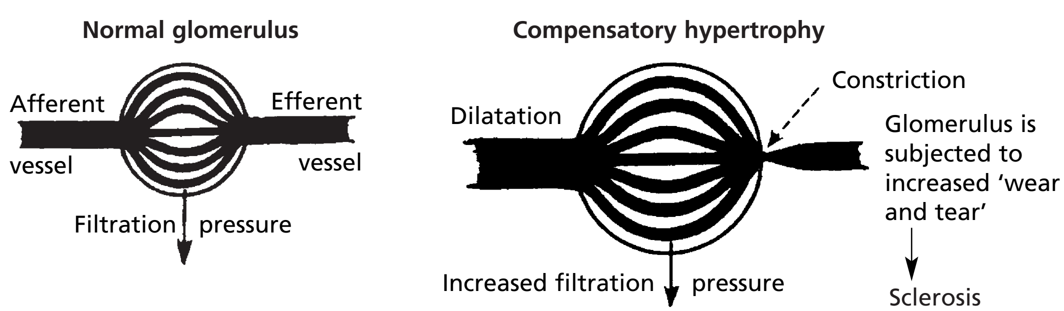
In many cases the underlying cause cannot be determined.
The severity of renal failure is monitored by the serum urea, creatinine and by the glomerular filtration rate (GFR).

Chronic Kidney Disease

Stage 1 Slight Kidney damage
2 Mild decrease in kidney function
3 Moderate decrease in kidney function
4 Severe decrease in kidney function
5 Renal failure requires dialysis or transplantation

↓ The rate of decline depends on the underlying cause

Compensatory mechanisms:
As nephrons are lost, the surviving nephrons show (1) COMPENSATORY HYPERTROPHY and are (2) CONTINUALLY ACTIVE with no 'down time'. (In the normal kidney, the nephrons do not all function simultaneously.)



Effects of chronic renal failure:

1. **WATER and ELECTROLYTE BALANCE**

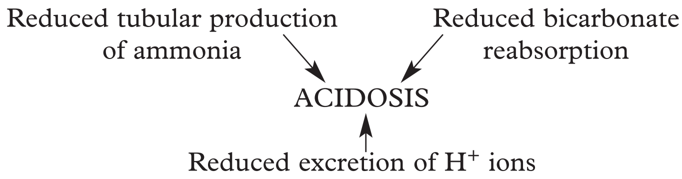
↓ Glomerular filtration rate → Retention of Na^+ → Hypertension
Retention of Na^+ → Retention of water
Loss of tubular resorptive power → Retention of water
Loss of tubular resorptive power → ↓ Excretion of K^+ → Hyperkalaemia → Cardiac arrhythmias

Urine concentration is lost.

CHRONIC RENAL FAILURE

Effects of Chronic Renal Failure (*continued*)

2. **DISTURBANCE OF ACID–BASE BALANCE**



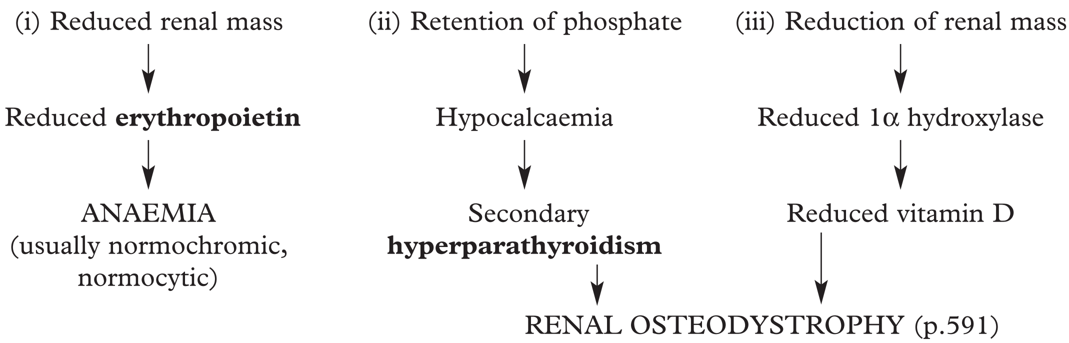
3. **URAEMIA**

The kidney also fails to excrete nitrogenous waste products, which accumulate. Although urea concentrations rise and are used to monitor renal function, retention of urea is not in itself harmful.

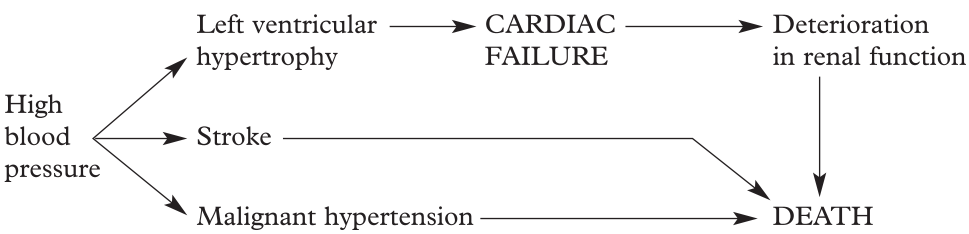
In uraemia, patients are lethargic. Anorexia, nausea and vomiting are common, with confusion, convulsions and death.

4. **HORMONAL ABNORMALITIES**

Three main hormones are involved: Erythropoietin, parathyroid hormone and vitamin D.



5. **HYPERTENSION** – This is almost inevitable and several consequences are possible.



6. **Fibrinous exudates**, e.g. **fibrinous pericarditis, 'uraemic pneumonitis' with pleural exudate.**
7. **Haemorrhagic ulcers** of the gastro-intestinal tract.
8. **Depression of immunological reaction.** Infections are common and will in turn affect renal function.

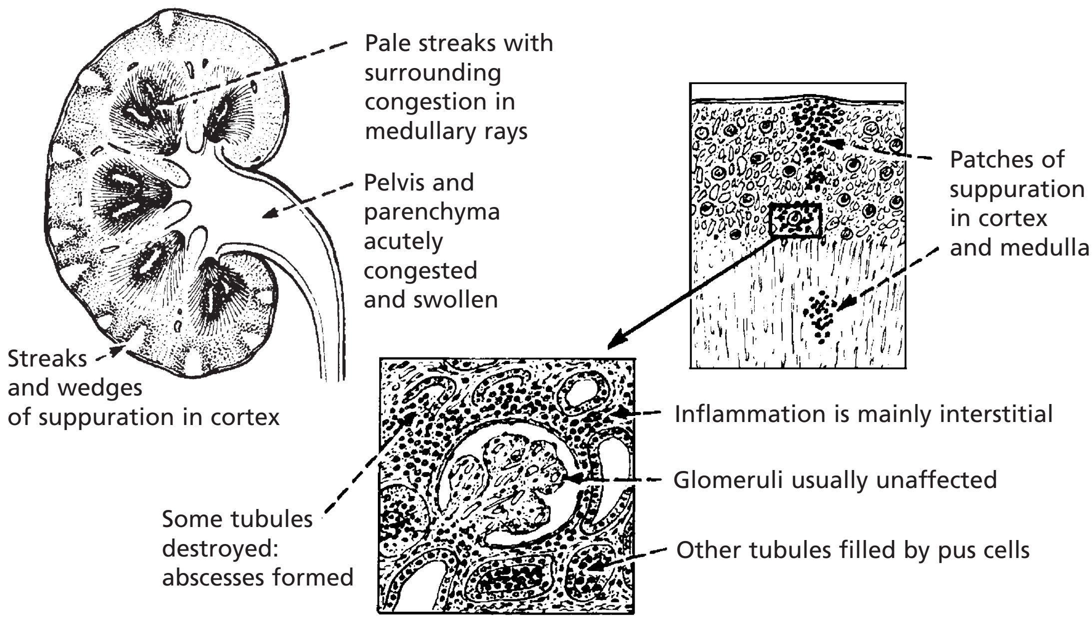
INFECTIONS OF THE KIDNEY AND URINARY TRACT

The kidney can become infected through 2 main routes.

(1) **Ascending infection** usually associated with **lower urinary tract infection** (obstruction and/or vesico-ureteric reflux are often present). This is by far the commoner route and gives rise to PYELONEPHRITIS.
(2) Blood borne (haematogenous) infection by pyogenic organisms (e.g. from septicaemia) or in tuberculosis (the latter now uncommon).

ACUTE PYELONEPHRITIS

This is an acute ascending pyogenic infection and the patient exhibits the usual general features of pyrexia, nausea, vomiting, headaches, rigors, etc., plus localising signs, e.g. frequency, dysuria, loin pain and sometimes haematuria.

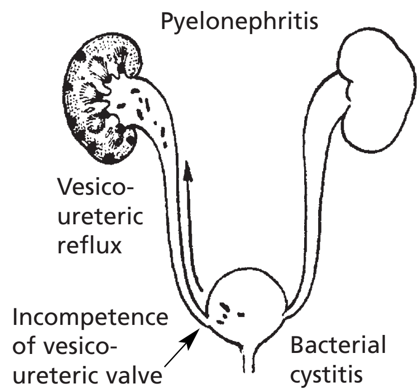


Bacteriology

Large numbers of bacteria are found in the urine, several hundred thousand per ml in the acute phase.

The commonest infecting organism is *Escherichia coli*, but other faecal bacteria may also be found, e.g. proteus, *Streptococcus faecalis*.

ACUTE PYELONEPHRITIS



Causes
In women, cystitis is common, particularly in the sexually active. Ascending infection is often provoked by vesico-ureteric reflux during micturition. Pyelonephritis is common in pregnancy.

In men, urinary tract obstruction is usually found, typically due to prostatic enlargement.

A number of causes of obstruction are seen in both sexes e.g. calculi or tumours in renal pelvis, tumours pressing on ureter, calculi in ureters and tumours of bladder.

Influence of urinary tract obstruction
Obstruction of the urinary tract acts in 3 ways to promote infection:

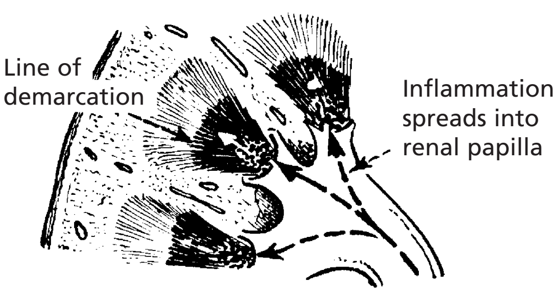
1. The urine tends to stagnate and encourages growth of bacteria.
2. A tendency to vesico-ureteric reflux during micturition develops especially when cystitis occurs.
3. Catheterisation is commonly carried out in these cases and can introduce infection. In this case the infection is likely to be mixed.

Progress The possibilities are as follows:

Acute pyelonephritis → Perinephric abscess | Papillary necrosis | Healing | Recurrence | Chronic pyelonephritis

Perinephric abscess and papillary necrosis are now rare due to specific antibiotic therapy.

Papillary necrosis (maximal at the kidney poles) is most likely to occur in cases associated with urinary obstruction, diabetes, analgesic nephropathy (e.g. aspirin), sickle cell anaemia and severe hypotension.

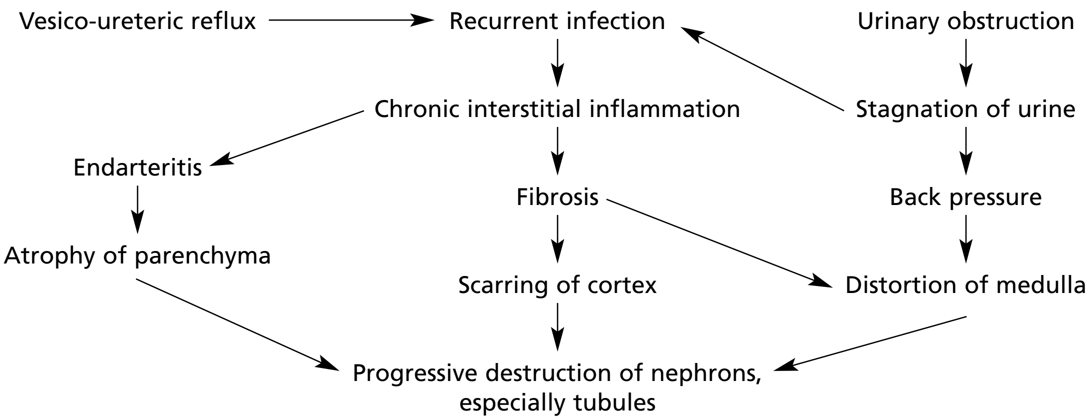


Inflammation spreads into renal papilla → Intense interstitial inflammation
↓
Thrombosis of vessels and necrosis of renal tissue
↓
Destruction of collecting ducts and calyces

This can lead rapidly to renal failure.

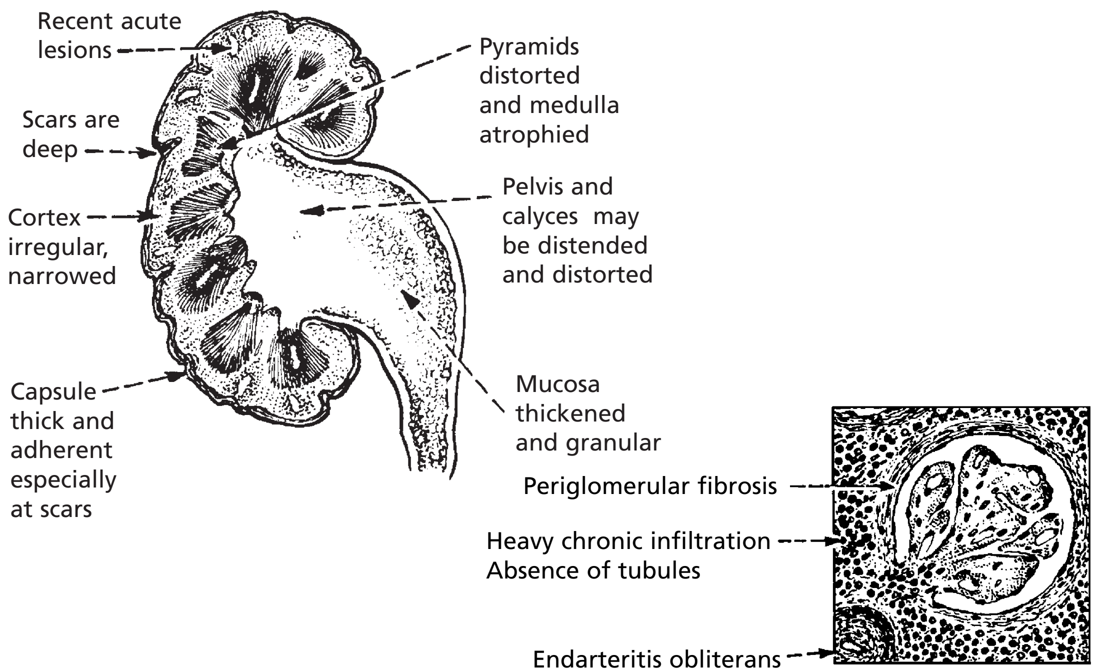
CHRONIC PYELONEPHRITIS

Chronic pyelonephritis is essentially the result of repeated attacks of inflammation and healing. Vesico-ureteric reflux in early life, often associated with congenital anomalies of the urinary tract, is now regarded as important. The process can be visualised as follows:



Kidney function may be further diminished by the onset of hypertension. In cases with urinary obstruction, the external size of the kidney may remain normal or even be increased. Those with no underlying abnormality, commoner in the female, show progressive contraction of the kidney which becomes greyish white.

Microscopically, there is interstitial fibrosis, inflammation and loss of parenchyma.



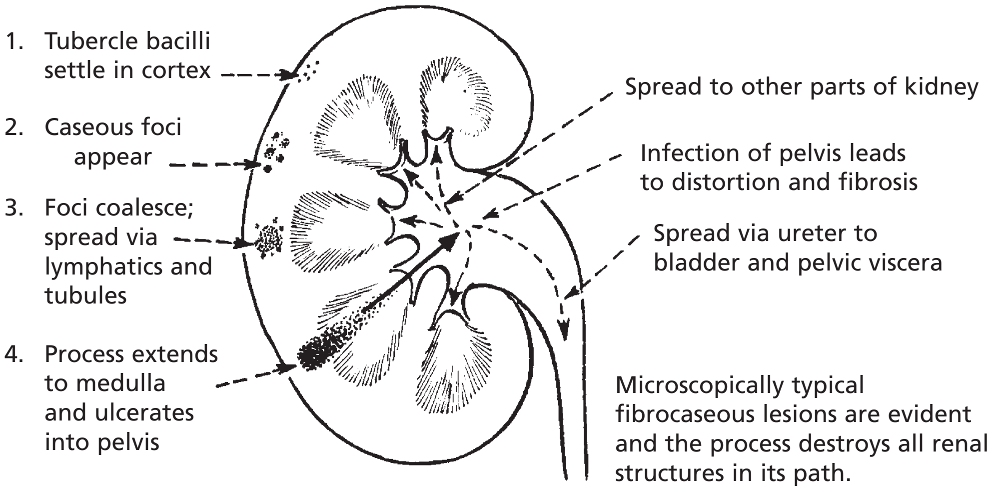
Depending on the cause, only one or both kidneys may be affected to variable degrees (c.f. chronic glomerulonephritis).

TUBERCULOSIS OF THE KIDNEY

Uncommon in many Western countries. It is due to **blood spread of infection** from another site, e.g. the lungs. Even less commonly, there may be an ascending infection from some other part of the genitourinary system, e.g. epididymis.

As usual, the tuberculous process develops slowly and lesions in the lungs which are the source of infection may have healed and disappeared by the time kidney damage is clinically apparent. The disease is commonly unilateral.

Stages



Clinical features

The patient may show the general features of tuberculous infection – fever, night sweats and loss of weight. Lumbar discomfort or pain, dysuria and haematuria can develop. Mycobacteria can usually be demonstrated in the urine either on direct microscopic examination or by culture.

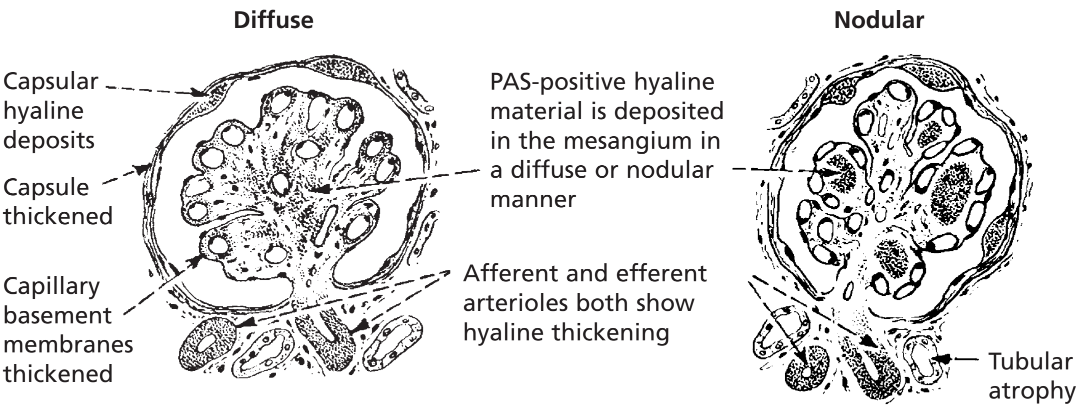
INTERCURRENT RENAL CONDITIONS

DIABETES

Renal complications are common in diabetes. Up to 30% of diabetics develop proteinuria, usually after many years and may go on to chronic renal failure.

The renal lesion is a special form of the 'small vessel disease' seen systemically in insulin dependent diabetes, e.g. diabetic retinopathy. Rarely similar changes can be seen in non diabetics.

Diabetic glomerulosclerosis. This takes one of two forms:



The basement membrane thickening is due to deposition of abnormally glycosylated proteins. The nodular form is often termed the Kimmelstiel–Wilson lesion. Progressive closure of capillaries can occur together with fibrous obliteration of the capsular space and the whole glomerulus. Haemodynamic changes, especially hyperfiltration, lead to sclerosis. Secondary tubular atrophy follows.

Clinical effects

Screening for microalbuminuria is important to detect early disease. Proteinuria may result in the nephrotic syndrome. Hypertension leads to further renal damage: control of blood pressure, and of diabetes itself, is important to delay the onset of renal failure. Inhibitors of angiotensin activity are particularly effective.

Pyelonephritis

This is common in diabetes and may be complicated by papillary necrosis.

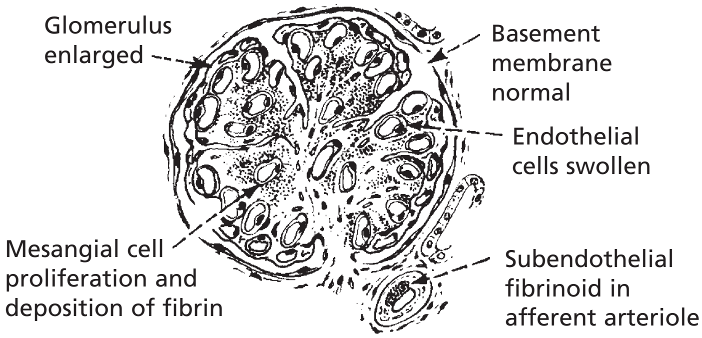
Atheroma

This disease is common in the renal arteries and their branches in diabetes. It increases the renal ischaemia.

RENAL FUNCTION AND PREGNANCY

Four conditions affecting renal function may arise in pregnancy.

1. **Acute pyelonephritis** is relatively common, possibly due to (a) the effects of uterine pressure on the ureters and (b) relaxation of smooth muscle allowing ureteric dilatation and reflux.
2. **Pre-eclampsia and eclampsia.** This is a syndrome characterised by hypertension, increasing unselective proteinuria and oedema. Placental ischaemia with stimulation of vasoconstriction leads to disseminated intravascular coagulation (DIC). The main kidney lesion is glomerular; tubular changes are secondary.



EM examination shows mesangial deposits of fibrin, fibrinogen, IgM and complement.

The lesion appears to resolve rapidly after birth.

Acute tubular necrosis, is associated with complications of pregnancy causing SHOCK, e.g. septic abortion, retroplacental haemorrhage and postpartum haemorrhage.

In more severe cases **bilateral cortical necrosis** may occur especially if disseminated intravascular coagulation (DIC) is superadded.

Severe liver and cerebral damage may also occur.

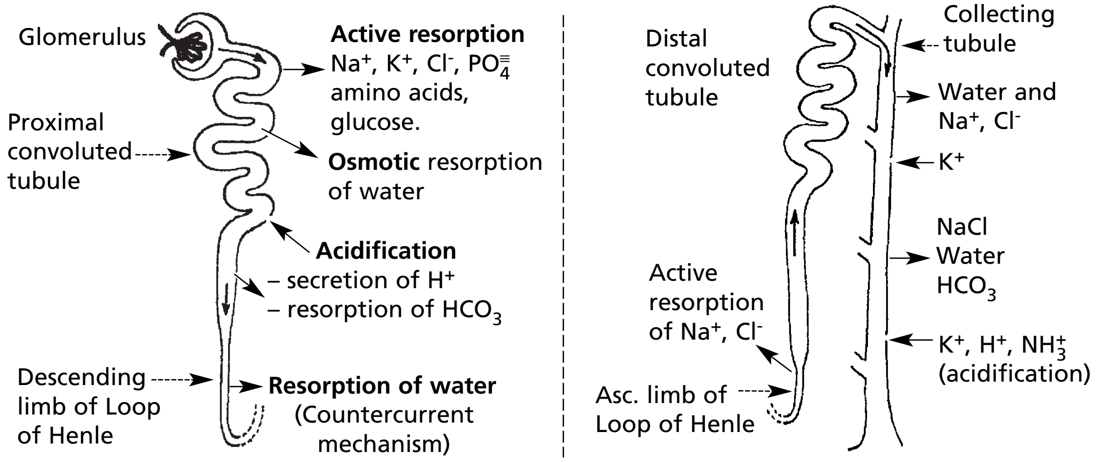
RENAL TUBULE – STRUCTURE AND FUNCTION

The renal tubules modify the glomerular filtrate. Initially isotonic and neutral, it becomes hypertonic and quite strongly acid. Within 24 hours, 180 litres of filtrate are reduced to 1.5 litres of urine. The main functions of this process are:

(a) to get rid of waste products, particularly those of protein metabolism.
(b) to aid in maintaining the normal acid–base balance.
(c) to conserve fluid, electrolytes and other essential substances.

Three mechanisms are involved:

1. Active absorption of substances from the filtrate by the tubular epithelium.
2. Passive interchange between the filtrate and the interstitial tissues to maintain osmotic equilibrium.
3. Secretion by the tubular epithelium.



Note: Active reabsorption requires energy, and there is a limit to the capacity of the process – maximal tubular capacity (Tm). When this is exceeded, the particular substance involved will appear in the urine. Glucose is an example. In diabetes, the amount of glucose in the filtrate far exceeds the absorptive capacity, and glycosuria results.

Effects of tubular damage

Damage to the tubules results in gross biochemical changes.

1. Loss of mechanisms controlling balance of electrolytes, water and urea.
2. Upset in acid–base balance.
3. Loss of substances in urine normally completely or almost completely reabsorbed – glucose, potassium, amino acids.

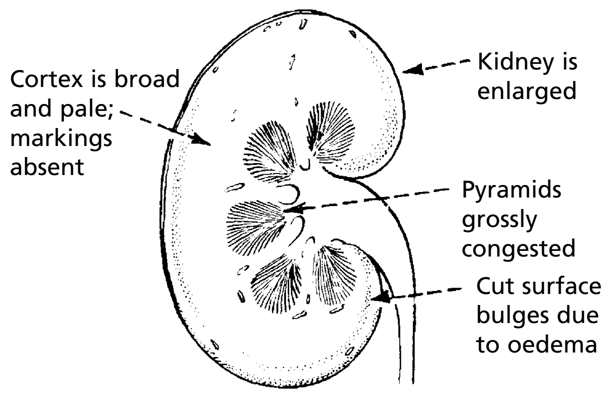
Glomerular lesions and pathological changes in the renal pelvis also upset tubular function by interfering with blood supply.

ACUTE KIDNEY INJURY (AKI) (ACUTE TUBULAR NECROSIS)

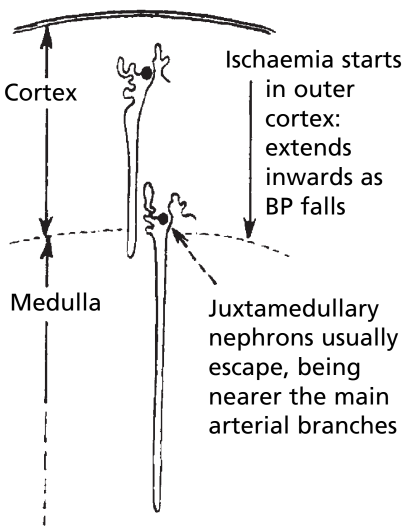
This arises in 2 circumstances:

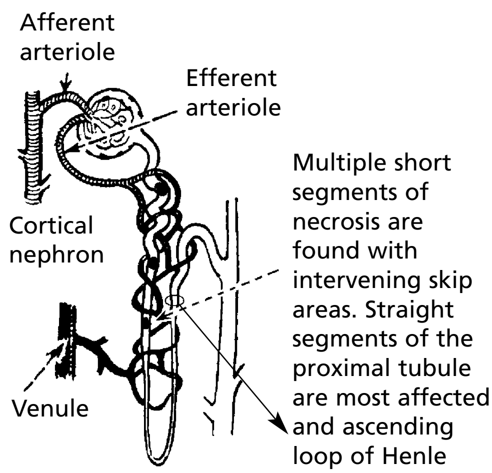
1. Due to ischaemia during a state of shock, e.g. due to haemorrhage, burns, trauma, acute intestinal obstruction, incompatible transfusion and acute pancreatitis.
2. Nephrotoxic: Due to directly toxic substances, e.g. carbon tetrachloride, cis-platinum, lithium, mercury, and various drugs, e.g. antibiotics, radiocontrast drugs.

The gross appearance of the kidneys is the same in both groups.



Ischaemic Acute Kidney Injury (AKI)
The lesions are the result of ischaemia, and this determines the part of the kidney affected and the portion of the tubule damaged.



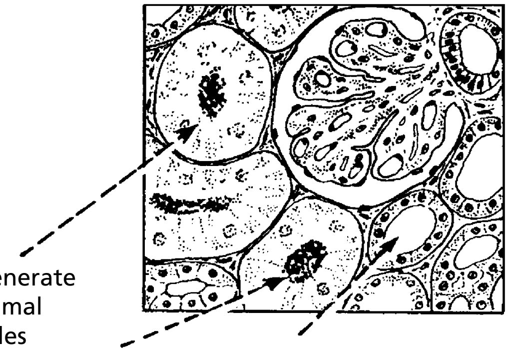


Casts are found in the distal tubules, consisting largely of Tam–Horsfall protein and plasma proteins.

ACUTE KIDNEY INJURY (ACUTE TUBULAR NECROSIS)

Toxic AKI

The lesions are evenly distributed, affecting all nephrons. They are maximal in the proximal tubules and are the direct result of the toxin, the action of which is intensified by the concentrating activity of the tubule.



Clinical effects

There are two clinical phases:

1. ***Oliguria***

The glomerular filtration rate is greatly reduced due to reduced renal blood flow. Unselective reabsorption of the filtrate occurs through the damaged tubule. The effects are:

Reduced GFR → Retention of non-protein nitrogenous wastes → Uraemia

Reduced GFR → Retention of fluid

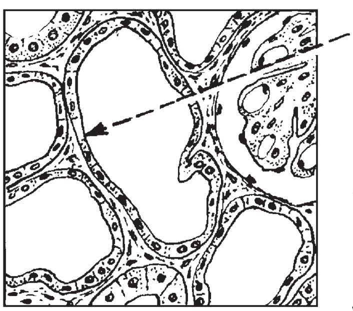
Tubular damage → Retention of fluid → Danger of pulmonary oedema

Tubular damage → Upset in electrolyte balance → Hyperkalaemia → Possible cardiac arrest

Tubular damage → Acidosis due to inability to control hydrogen ion concentration of urine

2. ***Diuresis***

This occurs following healing of the lesions. The damaged tubular epithelium is replaced by a simple type which has not yet developed selective activities. Large volumes of dilute urine are passed.



The clinical results are:

Absence of concentration → Continued retention of non-protein nitrogenous wastes

Absence of concentration → Upset in acid–base balance

Absence of concentration → Loss of electrolytes including K⁺ → Possible cardiac irregularity

Absence of concentration → Loss of fluid → Dehydration

Loss of fluid → hypokalaemia → Possible cardiac irregularity

The tubular epithelium has a great capacity for regeneration and ultimately regains its selective powers and the prognosis is good.

TUBULO-INTERSTITIAL DISEASES

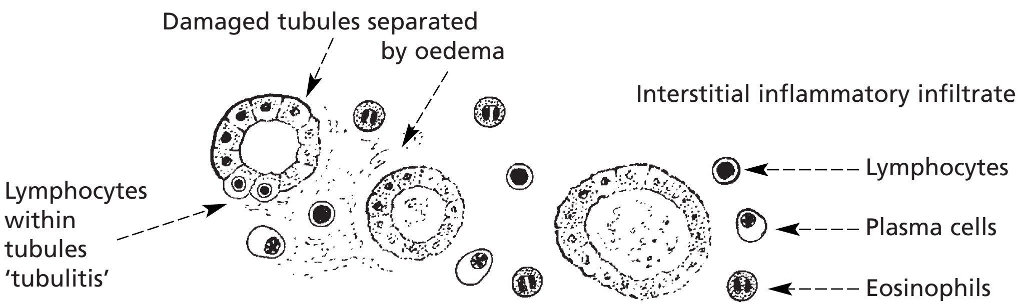
In this group of disorders there is damage to the renal tubules and to the interstitial tissues. The main forms are:

(a) Acute tubular necrosis
(b) Infection – Pyelonephritis } Pages 463, 470, 471
(c) Interstitial nephritis.
(d) Metabolic conditions – e.g. gout, nephrocalcinosis, hypokalaemia.
(e) Myeloma cast nephropathy.
(f) Renal tubular abnormalities.

TUBULO-INTERSTITIAL NEPHRITIS
There are two types – acute and chronic, both typically associated with an immunological reaction to drugs.

ACUTE: Symptoms develop 10–14 days after exposure to drugs e.g. methicillin and NSAIDs e.g. mefenamic acid. Patients are febrile, there is haematuria, proteinuria. Arthralgia is common. Renal impairment varies in severity – may cause ACUTE RENAL FAILURE.

Pathology



Prognosis (i) Complete remission may follow withdrawal of drug and/or treatment with steroids.
(ii) Continuing exposure ⟶ chronic renal impairment.

CHRONIC: Long-standing interstitial nephritis leads to interstitial fibrosis, inflammation and continuing tubular damage with tubular loss and atrophy. Many patients present with chronic renal failure. 'Balkan nephropathy' found in the river Danube valley is due to ingestion of aristolochic acid, found in herbal remedies.

ANALGESIC NEPHROPATHY
This is a distinctive disorder caused by long term exposure to analgesics e.g. phenacetin (historically) and NSAIDs. Interstitial inflammation and tubular damage may proceed rapidly to papillary necrosis (p.463).
There is an associated increased risk of transitional cell carcinoma of the kidney and ureter (p.481).

Both minimal change and membranous glomerulonephritis may complicate NSAID therapy.

METABOLIC TUBULAR LESIONS

These are due to metabolic defects.

High plasma concentration of metabolite → Appearance in glomerular filtrate → Concentration and precipitation

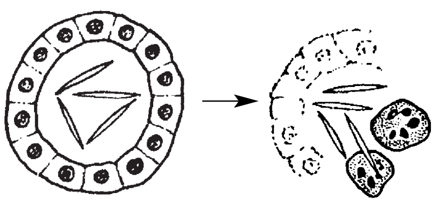
Concentration and precipitation → Necrosis of tubules → Interstitial fibrosis → Progressive renal damage and failure

Concentration and precipitation → Formation of calculi → Secondary inflammation and other complications → Progressive renal damage and failure

The following are some examples:

(a) **Hypercalcaemic nephritis**
Calcium is deposited in tubular epithelial cells with subsequent fibrosis and calcification – **nephrocalcinosis.**
The usual causes of hypercalcaemia are malignant tumours, primary hyperparathyroidism, hypervitaminosis D and sarcoidosis.

(b) **Urate nephropathy** occurs in patients with long standing hyperuricaemia and **gout**.
Increased primary secretion of uric acid leads to uric acid crystal formation in the acid environment of the distal tubule. Renal uric acid stones can occur.



The tubular wall is destroyed → Interstitial giant cell reaction and fibrosis; Nephron loss

(c) **Myeloma cast nephropathy**
This is dealt with on pages 433 and 434.

RENAL TUBULAR ACIDOSIS
The tubules, either due to an inherited defect or to damage secondary to other renal diseases, are unable to produce an acid urine.

There are 2 main forms:
1. In Type I the defect is in the distal tubule.
2. In Type II the function of the proximal tubule is abnormal and there are usually other abnormalities in addition to acidosis, e.g. in the Fanconi syndrome there is aminoaciduria, glycosuria and hypophosphataemia.

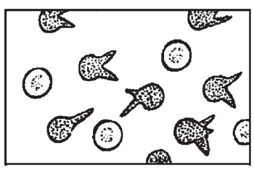
THROMBOTIC MICROANGIOPATHIES (HAEMOLYTIC URAEMIC SYNDROME)

This is a rare complication of many conditions.

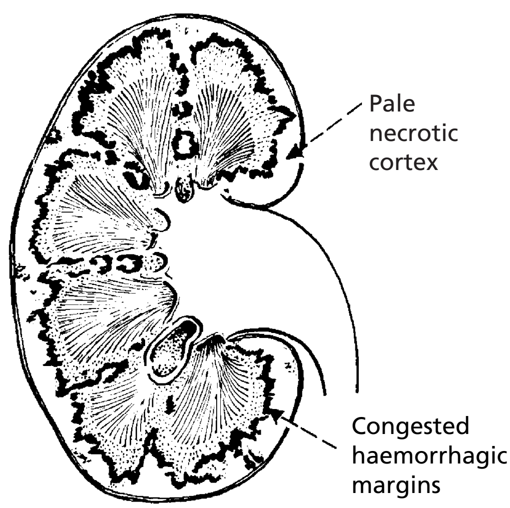
Drugs → Endothelial injury
Toxins → Endothelial injury
Malignant hypertension → Endothelial injury

Endothelial injury
↓
Activation of clotting mechanism
↓
Disseminated intravascular coagulation → Thrombocytopenia
↓
Fibrin thrombi in small vessels

Fibrin thrombi in small vessels → Haemolysis – typical fragmented burr cells in blood
Fibrin thrombi in small vessels → Ischaemic lesions in organs especially the kidney and brain



The renal lesions are similar to those seen in malignant hypertension. There is fibrinoid necrosis of the afferent arterioles and capillaries of the glomeruli, resulting in tubular necrosis. In the most extreme cases, bilateral cortical necrosis of the kidneys may occur. Clinical manifestations include renal failure, haemolytic anaemia, hypertension, and sometimes purpura with thrombocytopenia.



Aetiology

Activation of the clotting system can occur in many widespread circumstances:

1. In children there is a close association with alimentary infections: particularly by *E. coli* 0157 which produces a verocytotoxin.
2. Shock, e.g. following abruptio placentae in pregnancy, endotoxic shock.
3. Malignant hypertension.
4. Drugs, e.g. immunosuppressives.

PATHOLOGICAL COMPLICATIONS OF RENAL REPLACEMENT THERAPIES

The prognosis of end-stage renal failure has been greatly improved by (1) Dialysis and (2) Renal Transplantation. The following possible pathological complications are important:

1. Dialysis

(a) *Haemodialysis*

- (i) ***Local*** – infection and thrombosis at site of vessel access.
- (ii) ***Systemic*** – aluminium toxicity: historically, severe dementia or severe osteomalacia was caused by using water containing excess aluminium. Aluminium and other impurities are now removed.
  Amyloidosis largely affecting osteoarticular tissues (e.g. carpal tunnel syndrome: joint stiffness bone cysts) due to raised circulating β_2 microglobulin. Visceral involvement is rare and late.

(b) ***Continuous Ambulatory Peritoneal Dialysis (CAPD)*** – infective peritonitis: especially due to Staphylococci, Gram –ve organisms and fungi.

Sclerosing peritonitis is a non-infective complication with fibrous thickening of the peritoneum; this may result in small bowel obstruction or necrosis.

2. Renal transplantation

Rejection is the main complication, depending on the extent of HLA matching between donor and recipient. The Banff classification is used to type rejection of which there are four forms:

(a) *Hyperacute rejection* – within minutes or hours
Pre-existing antibodies against donor HLA or ABO → Binding to endothelial cells → Thrombosis and necrosis

(b) *Acute cellular rejection* – within days to months
Cell mediated response against donor cells → Interstitial lymphocytic infiltrate and 'tubulitis' → Tubular destruction

(c) *Acute vascular rejection* – days to months
Cell mediated immune response to epithelial cells → Infiltration of vessel wall by lymphocytes 'endotheliitis' → Thrombosis and necrosis

(d) *Chronic rejection* – months to years
Continuation of immune attack → Vascular occlusion, glomerular sclerosis → Ischaemia and renal failure

Other complications

1. Cyclosporin and tacrolimus toxicity
2. Opportunistic infections
3. Increased incidence of tumours, particularly LYMPHOMAS

} Associated with therapeutic immuno-suppression.

Note: Many lymphoproliferative disorders are due to Epstein–Barr virus infection and some respond to reduction in immuno-suppressive therapy.

4. Recurrence of original renal disease, e.g. IgA nephropathy in transplanted kidney.

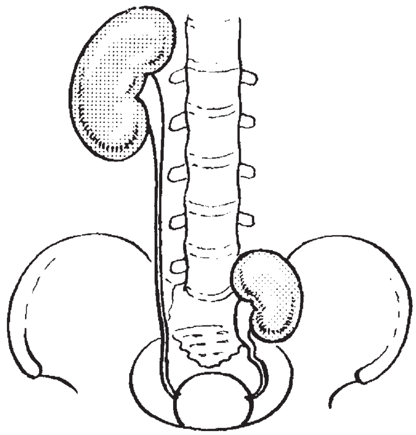
CONGENITAL DISORDERS

There are many forms of malpositions and malformations of the kidney:

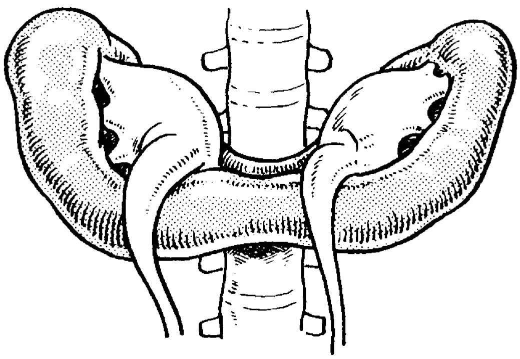
1. **Ectopic kidney (pelvic kidney)**

One or both kidneys fail to reach the normal adult position. The condition causes difficulty:

(a) During childbirth
(b) In differential diagnosis of pelvic neoplasms and infections
(c) When the renal artery originates at the normal level and the long vessel creates problems in arterial supply.



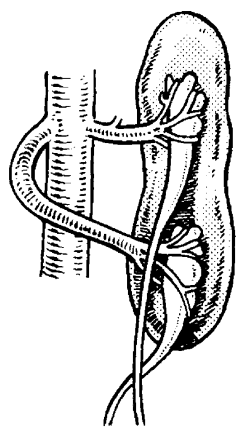
2. **Fusion of kidneys**



This is usually partial, producing the so-called 'horse-shoe' kidney. The ureters may be partially obstructed leading to hydronephrosis, infection and stones.

3. **Single kidney**

This may be a form of fusion and there may be two ureters. In other cases, there is absence (agenesis) of one kidney, usually the left. There is no interference with renal function unless, of course, the single kidney becomes diseased.



4. **Bilateral agenesis (Potter's syndrome)**

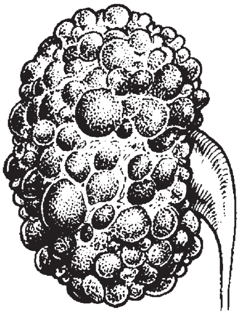
This is incompatible with life. The affected infants have a distinctive appearance, with low set ears, receding chin, parrot beak nose and wide set eyes.

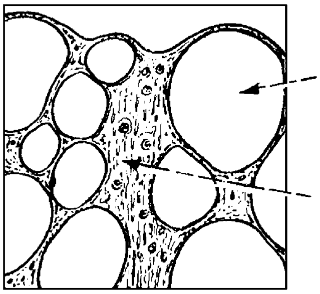
POLYCYSTIC KIDNEY DISEASE

This occurs in two main forms:

1. **Autosomal Dominant Polycystic Kidney Disease (ADPKD)**

This is relatively common, and accounts for 5–10% of cases of chronic renal failure. The kidneys are converted into a mass of cysts with loss of renal parenchyma.
It is an inherited autosomal dominant trait due to two genes, PKD-1 (85% of cases) which encodes a protein polycystin-1, and PKD-2 (15%) associated with milder disease.





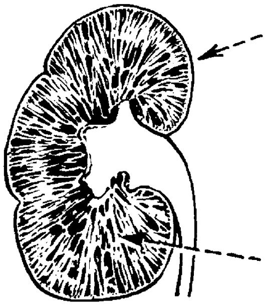
The precise defect is unclear but defects of the cilia of tubular epithelial cells appear responsible. There is cyst formation in some of the collecting tubules, causing a mixture of normal and abnormal nephrons. Cystic change develops after birth and is progressive, resulting in atrophy of normal nephrons by pressure.

Cysts also occur in the liver. Death from cerebral haemorrhage is more frequent than expected, partly due to the hypertension secondary to the kidney disorder and in some cases to Berry aneurysms of cerebral arteries.

It is usually discovered during 3rd and 4th decades.

2. **Autosomal Recessive polycystic kidney disease**

This is a rare condition, which may present in the perinatal period or later in childhood.

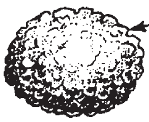


The nephrons are said to be normal in number and formation. Cystic dilatation is situated in the terminal branches of the collecting tubules. The disease, if severe, is incompatible with life, and death occurs shortly after birth. It is an autosomal recessive trait due to mutations of the *PKHD-1* gene. Congenital hepatic fibrosis often dominates in children who survive infancy.

URINARY CALCULI

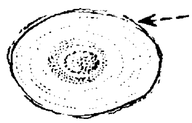
Stones may form in the renal pelvis, ureter or bladder.

Four basic types of renal calculi are recognised.



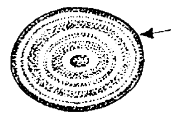
Surface is rough; colour brown, probably due to old blood pigment

(1) **Calcium oxalate** (~80%)



Flaking surface, greyish white

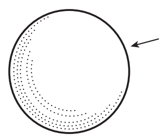
(2) **Triple phosphates** (magnesium phosphate ammonium) (15%)



Smooth light brown colour

(3) **Uric acid and urates** (5%)

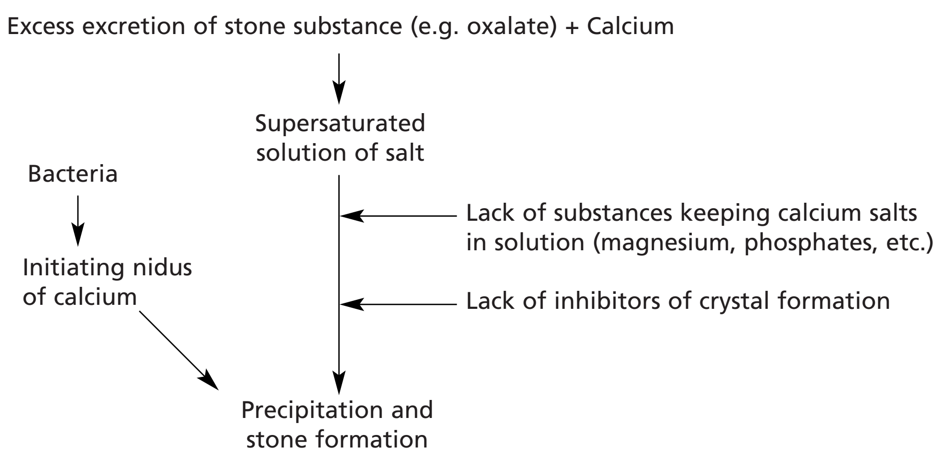
(4) Cystine in primary cystinuria (1%)



Smooth round stone

Commonly the stones are mixed.

Mode of formation. There are two steps – *nucleation* followed by *aggregation*:



Predisposing factors

1. **Urinary pH**. Urate and oxalate stones form in an acid urine; phosphate stones in alkaline urine.
2. **Dehydration** – causing increased urinary concentration.
3. **Stasis.** Obstruction to urine flow encourages salt precipitation.
4. **Infection** is one of the most important factors.

URINARY CALCULI

Predisposing factors (*continued*)

5. **Metabolic factors.** These can operate by altering the pH of the urine and especially by increasing the output of substances, e.g.
   (a) Hypercalcuria and hyperphosphaturia. These may be caused by:
      Hyperparathyroidism, primary or secondary to renal failure
      Vitamin D overdosage
      Diet, e.g. excessive milk and alkalis over years in peptic ulcer cases
      Immobilisation leading to loss of calcium from bones.
   (b) Oxaluria. Due to:
      Congenital metabolic defect (primary oxaluria)
      Intestinal over absorption in enteric diseases and vegetarians.
   (c) Urate excess.
   (d) Rare stones, e.g. cystine, xanthine, are related to inborn metabolic defects.

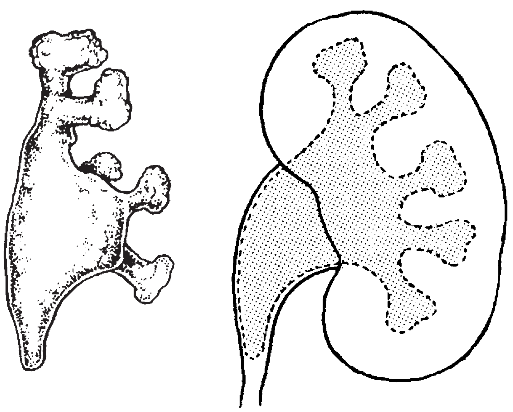
Effects
This can lead to:

- Renal colic
- Hydronephrosis
- Infection, e.g. pyelonephritis.

With the development of stasis and infection, further stone formation is encourgaged:

Staghorn calculus
This large single stone is associated with suppuration and ulceration of the pelvis and calyces. It is composed mainly of phosphates.

Stones and infection in the pelvis can lead to squamous metaplasia of the epithelium. In a few instances this may develop into squamous carcinoma.



BLADDER CALCULI
These may have passed down the ureter. In the bladder they can increase greatly in size, due to the deposition of phospates. Cystitis is common. Stones may actually form in the bladder when there is urethral obstruction and chronic cystitis.

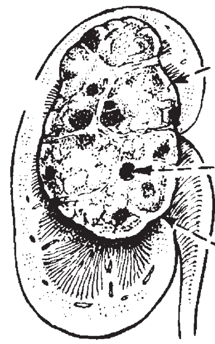
TUMOURS OF THE KIDNEY

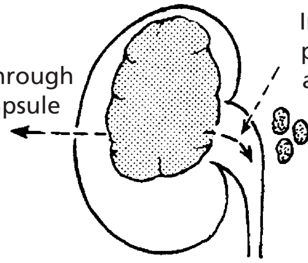
MALIGNANT TUMOURS

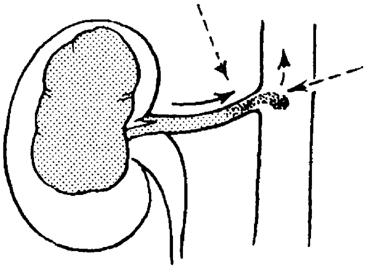
Three are of importance: renal cell carcinoma, transitional cell carcinoma and nephroblastoma.

Renal cell carcinoma

This is the commonest (90%) primary malignant renal tumour and arises from tubular epithelium. It has a typical appearance.









Aetiology: Renal cell carcinoma is associated with:

(a) Cigarette smoking,
(b) Obesity,
(c) Cystic change in patients on haemodialysis,
(d) Genetic predisposition, e.g. the von Hippel–Lindau syndrome (renal cysts, cerebellar haemangioblastoma) – associated with a gene on chromosome 3.

Systemic effects

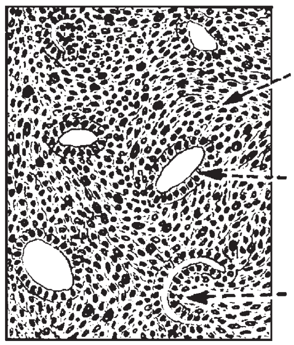
Patients with renal carcinoma may have:

(i) Hypercalcaemia – parathyroid related hormone peptide production (PTHrP).
(ii) Hypertension – increased renin production by tumour or in adjacent kidney.
(iii) Polycythaemia – increased erythropoietin.

TUMOURS OF THE KIDNEY

Transitional cell carcinoma of the renal pelvis is discussed on p.483.

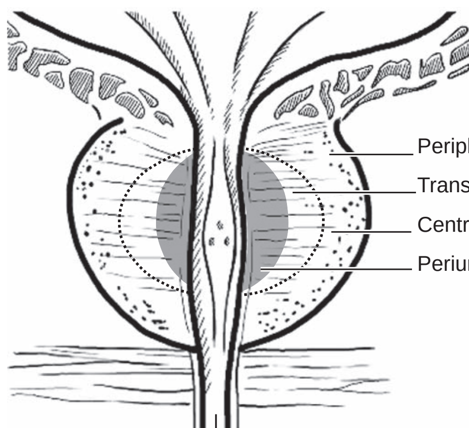
Nephroblastoma (Wilms' tumour)
This is one of the commonest malignant tumours of childhood usually presenting between 2 to 5 years. About 10% are bilateral. It is an embryonic type of tumour derived from 'nephrogenic rests', and forms a large well-circumscribed growth which rapidly invades blood vessels, giving rise to pulmonary secondaries. With modern therapy 90% long-term survival rates are achieved.



Mutation of the Wilms' tumour gene (WT-1) on chromosome 11 and a variety of other genes appear to be responsible for the development of this tumour.

BENIGN TUMOURS

1. **Oncocytoma.** This benign epithelial tumour accounts for 5% of surgically removed tumours. It arises from cells of the collecting ducts. The cells are large with eosinophilic nuclei due to many mitochondria.
2. **Papillary adenoma.** This is a small (< 5 mm) nodular proliferation of tubular type epithelium.
3. **Angiomyolipoma.** This mass of fat, blood vessels and smooth muscle may occur sporadically or in tuberous sclerosis.

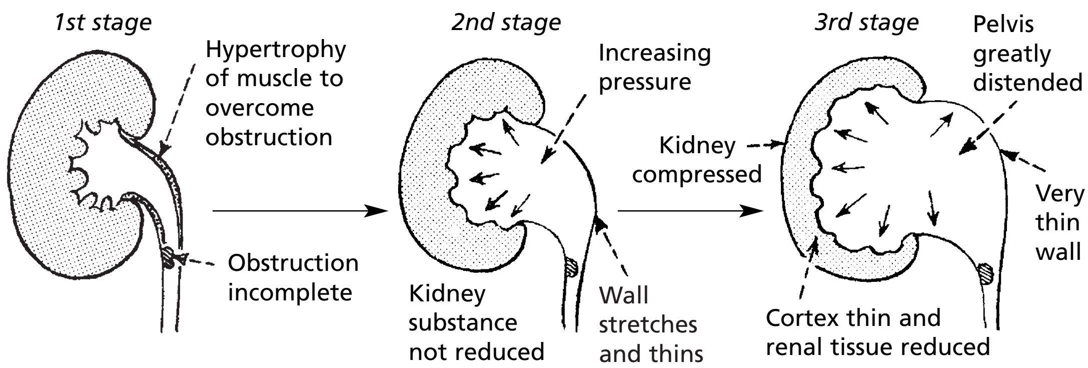


DISEASES OF THE URINARY TRACT

The urinary tract is a collecting and discharge system. There are 4 main pathological processes affecting its function: (1) obstruction, (2) infection, (3) calculus formation and (4) neoplastic disease.

Obstruction
Acute obstruction, if complete, causes rapid cessation of urine production. If both kidneys are involved, renal failure quickly follows. Chronic obstruction is more common and leads to anatomical changes, with sequels.

Hydronephrosis
This is a dilatation of the renal pelvis and calyces, due to chronic incomplete or intermittent obstruction.



Microscopically, there is tubular atrophy and glomerular scarring. Superimposed infection is common and aggravates the renal damage.

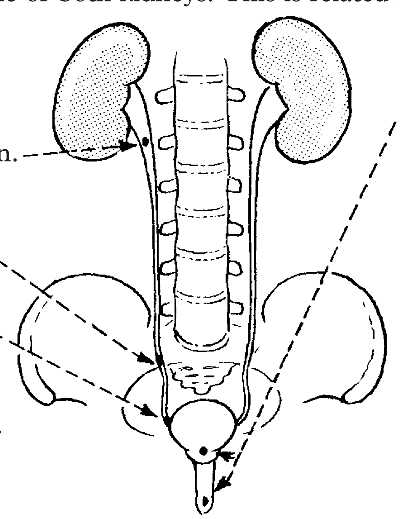
Aetiology
The condition may affect one or both kidneys. This is related to the site of obstruction.

Unilateral obstruction:
above the bladder

Common sites:
1. Pelvi-ureteric junction.
2. At pelvic brim.
3. At entrance to bladder.

Causes:
1. Calculus.
2. Tumour growth.
3. Inflammatory stricture.
4. Congenital abnormality.

Gross hydronephrosis is more commonly unilateral.



Bilateral obstruction:
in or around bladder or urethra. The ureters are also affected and become dilated and tortuous.

Causes:
1. Prostatic enlargement.
2. Tumour of bladder.
3. Urethral stricture.
4. Pelvic neoplasm.
5: Retroperitoneal fibrosis.

URINARY TRACT INFECTION

Acute cystitis
The bladder shows the usual signs of inflammation. Small haemorrhages are common in the oedematous mucosa. The causes have already been discussed.

Chronic cystitis
This is the result of repeated attacks of acute cystitis, but it is usually associated with obstruction of the urethra causing stasis of urine.

Mixed infection including *B. proteus* is common and, together with urea-splitting organisms forming ammonia, result in an alkaline urine. Phosphates precipitate and can form crumbling whitish calculi.

Interstitial cystitis
This disorder usually affects women who complain of intermittent pain, frequency and dysuria without bacterial infection.

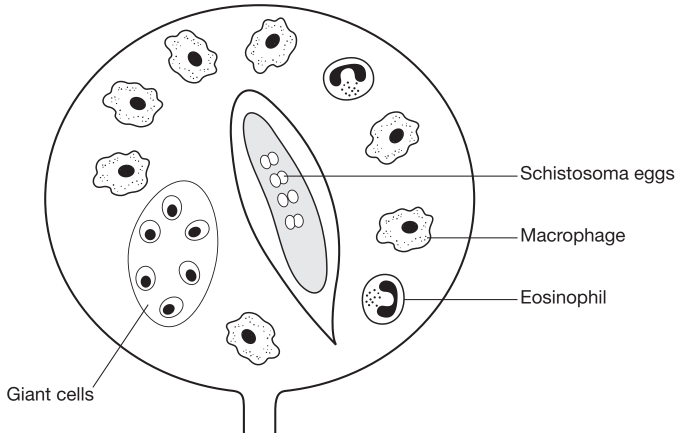
Mast cells are commonly seen in the mucosa which may show typical ulcers (Hunner ulcers). The cause is unknown.

Tuberculous cystitis
This is always secondary to a tuberculous infection elsewhere, usually in the kidney. Less commonly, the epididymis is the source of infection. Small tubercles form in the submucous layer, usually at the bladder base. These ulcerate and secondary infection is common.

Urethritis
Acute inflammation of the urethra is commonly due to the gonococcus, but another form is now more common in Western countries: so-called non-specific urethritis is often due to chlamydia infection.

In Reiter's syndrome, in addition to urethritis, there is arthritis and conjunctivitis.

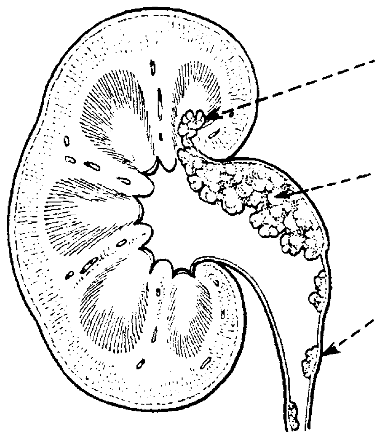
Schistosomiasis
Infection of the bladder with *Schistosoma haematobium* results in chronic granulomatous inflammation with urinary obstruction and haematuria. There is a strong association with the development of squamous cell carcinoma of the bladder.



TUMOURS OF THE UROTHELIUM

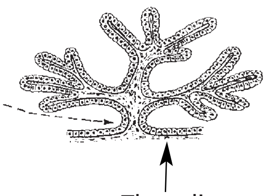
Transitional cell carcinoma
This tumour arises from the epithelium of the renal pelvis and is similar to the commoner transitional cell carcinoma of the bladder, with which it shares aetiological factors.

Patients usually present with haematuria.

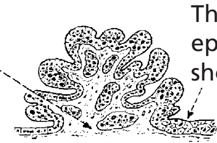


Transitional cell carcinomas occur in the bladder, ureters and renal pelvis. They arise from the stratified transitional epithelium lining the tract and are all considered to be CARCINOMAS but show a wide spectrum of malignant potential. They are graded I to III as follows, according to the World Health Organisation (WHO) classification. They can be papillary or solid in growth pattern.

GRADE I – These are usually **Papillary Tumours** with uniform, well-differentiated epithelial covering showing no mitotic activity, a slender stalk and delicate branching fronds. Haemorrhage is common.



GRADE II – These also are mainly **Papillary.** The epithelial cells show mitoses and nuclear pleomorphism.



GRADE III are often solid sessile tumours. They show marked nuclear pleomorphism, mitotic activity and aggressive growth. Ulceration and necrosis are common: invasion into the bladder muscle and lymphatic invasion are usual.

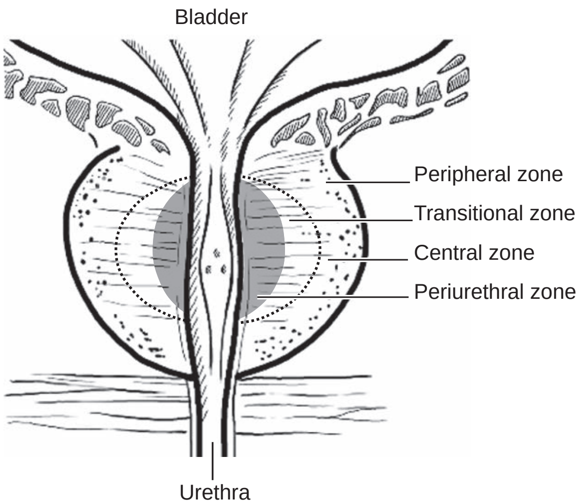
Squamous carcinoma and adenocarcinoma are rare tumours. Rhabdomyosarcoma may occur in the bladder in children.

(i) Urothelial tumours are often multiple and recurrence is common: long term surveillance is important.
(ii) Progression from a low grade to higher grades is frequent.

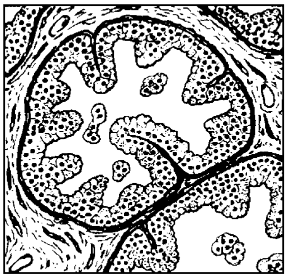
Aetiology
Smoking and analgesic abuse are important risk factors as is industrial exposure, e.g. rubber and dye industries. Infections with *Schistosoma haematobium* is associated with squamous carcinoma in the Middle East. Bladder carcinomas are an industrial hazard:
(a) In aniline dye manufacture due to beta-naphthylamine
(b) In the rubber industry
(c) In manufacturing processes involving benzene.

THE PROSTATE

The prostate surrounds the bladder neck and urethra. Although traditionally divided into five lobes, it is now regarded as having four major zones, which tend to be affected by different disorders.



Its internal structure is a series of branching glands in a fibromuscular stroma.



There are three main disorders of the prostate:

1. Prostatitis
2. Benign prostatic hyperplasia
3. Prostatic carcinoma.

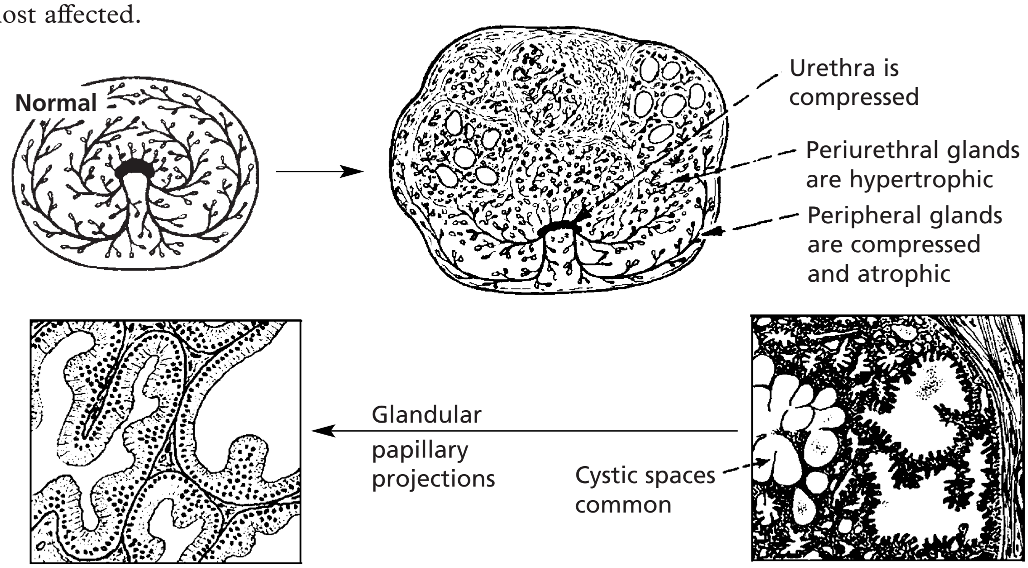
Prostatitis
There are three forms:

1. *Acute bacterial prostatitis* – associated with urinary tract infections – usually by Gram negative bacilli such as *E. coli.* Instrumentation, e.g. catheterisation may provoke the episode.
2. *Chronic bacterial prostatitis* – due to repeated urinary tract infections, usually by the same group of organisms.
3. *Chronic abacterial prostatitis* – the cause of this is unknown. The patient complains of urinary symptoms such as dysuria and frequency, low back pain and perineal discomfort.
4. *Granulomatous prostatitis* – can be seen in a variety of set ups, e.g. TB and following BCG therapy for bladder cancer. Ruptured ducts and acini may stimulate a granulomatous reaction which can simulate cancer.

DISEASES OF THE PROSTATE

Benign prostatic hyperplasia

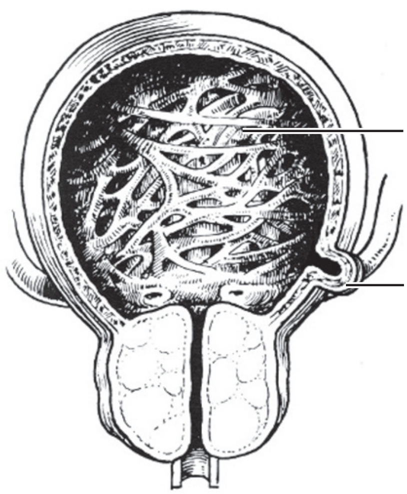
This is an extremely common finding in over 70% of men over 60 years. The prostate is enlarged often over 100 g (normal prostate 20 g). The transitional and periurethral zones are most affected.



Aetiology

Androgens are responsible for prostatic proliferation with conversion of testosterone to dihydrotestosterone by the enzyme 5α-reductase, found mainly in prostatic stromal cells. Use of 5α-reductase inhibitors is effective treatment in many cases; often combined with α adrenergic blockers.

Complications



Nodularity of lateral lobes with compression of urethra

Chronic retention leads to bladder dilatation and:

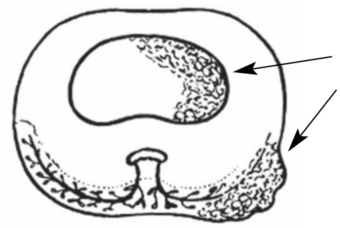
- Urinary tract infection due to stasis
- Hypertrophic muscle and diverticula
- Hydronephrosis
- Bladder stones.

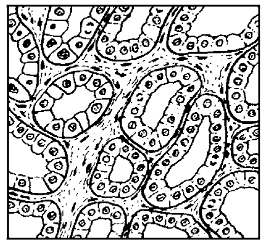
Prostatic enlargement leads to difficulty in urination:

- Acute retention of urine
- Frequency, nocturia, poor stream.

ADENOCARCINOMA OF THE PROSTATE

This is now the commonest cancer in men in the UK and a significant cause of cancer death. It is rare below the age of 40 and rises to very high prevalence in men over 80.





Histological grading:
The GLEASON system (Grades 2 through 10) indicates the degree of differentiation from (2) very well differentiated to (10) aggressive anaplastic tumours. Grading correlates well with prognosis.

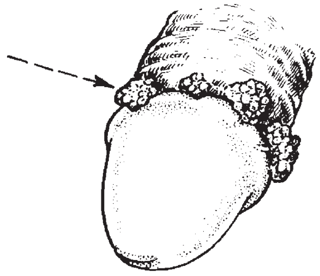
Spread
1. Direct spread occurs throughout the prostate and outwards to the pelviprostatic tissue.
2. Lymphatic spread is the main mode of extension. There is a rich lymphatic plexus and the perineural lymphatics are particularly affected. The pelvic nodes are invaded and subsequently the abdominal chain.
3. Bone metastases tend to be common, especially in the vertebrae. This is due to retrograde spread from the prostatic venous plexus to the vertebral veins. These secondaries are often characterised by the formation of new dense bone around them (osteosclerosis).

Biochemical tests
1. Prostatic specific antigen (PSA) measured in the blood is a useful diagnostic marker.
2. These tumours produce prostatic acid phosphatase and, when metastases are present, an increased level may be found in the blood. When bones are invaded, blood alkaline phosphatase may also rise due to osteoblastic activity.

Prostatic intraepithelial neoplasia (PIN), analogous to CIN (p.503), has been recognised as a pre-invasive stage of the disease. High grade PIN is strongly associated with development of invasive cancer.

DISEASES OF THE PENIS

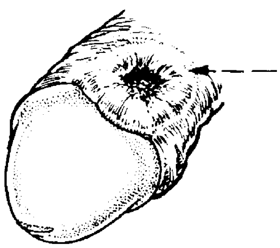
TUMOURS of the PENIS
Papillomatous proliferations (condylomata acuminata), usually arise in the coronal sulcus or glans. They are due to sexually transmitted infection by Human Papilloma Virus (HPV) Types 6 and 11, and are analogous to similar lesions in the female genitalia

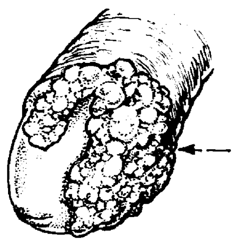


Peyronie's disease is a fibromatosis related to Dupuytren's contracture, which causes bending of the penis.

Precancerous lesions
Epithelial dysplasia and carcinoma-in-situ can affect the penis (Bowen's disease). This is related to HPV infection (Type 16).

Carcinoma of the Penis
Accounts for less than 1% of all male malignancy and affects middle-aged and elderly men. The site of growth is usually in the preputial area, often in the coronal sulcus, but it extends to involve the glans penis. Two forms of growth occur:





The growth spreads by the lymphatics to the regional (inguinal) nodes. Distant metastases occur late. The prognosis is reasonably good, 5-year survival rate being greater than 50%.

Aetiology
1. Males circumcised in childhood virtually never develop carcinoma; the risk is greatly increased in the presence of poor penile hygiene.
2. Human Papilloma Virus (HPV) Types 16 and 18 are the initiating carcinogens.

Inflammation
A wide variety of infections affect the penis, and are usually sexually transmitted. They include bacteria, e.g. syphilis and gonorrhoea, and viruses, e.g. genital herpes.

CANCER of the SCROTUM
This is a lesion which is rarely seen nowadays. Previously it was an occupational disease due to exposure to carcinogenic agents, e.g. soot, industrial oils, arsenic, etc.

DISEASES OF THE TESTIS

EPIDIDYMITIS AND ORCHITIS

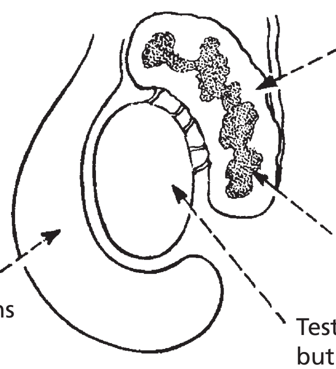
Acute inflammation due to bacteria is uncommon in these organs. Spread of urinary infection via the vas deferens does occasionally occur and may result in suppuration. Gonorrhoea and chlamydia are seen in young men.

In 20% of adult cases of mumps, the epididymis and testis become acutely inflamed. The condition is usually unilateral, but if bilateral there is a distinct danger of subsequent infertility.

Acute inflammation of the testis may be confused with **torsion**. Torsion generally occurs within the tunica vaginalis and leads to obstruction of the testicular vessels. Infarction results, with destruction of the tissue. Recurrent minor degrees of torsion can cause atrophy. Since the torsion may be bilateral, prophylactic surgery may reduce the risk of a second event.
Chronic inflammations are important, although rare, in this region.

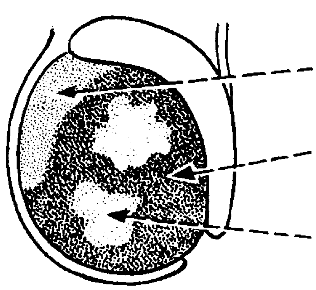
Chronic granulomatous orchitis
This is a condition of unknown origin. The testis is infiltrated by macrophages, plasma cells and lymphocytes. Atrophy of the germinal epithelium occurs and the testis becomes fibrotic.

Tuberculosis
The epididymis is affected first; spread may have come from the prostate or vas deferens.



Syphilis
Apart from the primary sore on the penis, the only other genital site involved is the testis. These are common in the tertiary stage. Two types of lesion are seen.

1. **Gumma**



2. **Granulomatous lesion** leading to scar formation with destruction of seminiferous tubules.

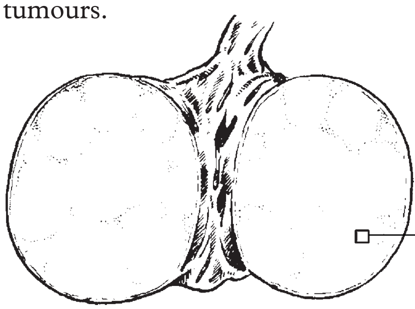
TUMOURS OF THE TESTIS

GERM CELL TUMOURS of the TESTIS

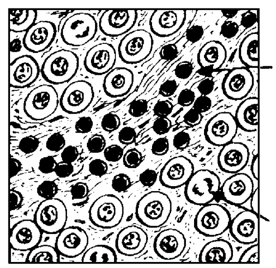
These tumours make up 2% of cancers in men and the incidence is rising steeply in Western countries. They are the commonest form of malignancy in young men. Tumours are more common in undescended testes.

The 2 main tumour types are SEMINOMA and TERATOMA.

Seminoma This corresponds to the dysgerminoma in the female. It is rare before puberty and has its peak incidence in adults in their 30s. It accounts for 50% of all testicular tumours.



The testis is uniformly enlarged; the surface is smooth. On section it has a uniform grey white appearance.



Spread is principally via the lymphatics and blood vessels along the spermatic cord.

The tumour is extremely radiosensitive and chemosensitive. Orchidectomy and adjuvant therapy give a >95% cure rate. In older men 'spermatocytic seminoma' is a rare variant but has an excellent prognosis.

Malignant teratoma (non-seminomatous germ cell tumour)

This type represents 35% of malignant testicular tumours. It takes origin from totipotent germ cells capable of differentiating into derivatives of ectoderm, endoderm and mesoderm. It is customary to classify them according to the degree and type of differentiation exhibited.

The tumours form a spectrum of well differentiated to anaplastic highly malignant growths and are classified in various ways. The following is often used:

MALIGNANT TERATOMA (MT)

SOMATIC DIFFERENTIATION → MTD (Malignant teratoma differentiated) WHO equivalent = mature teratoma; MTI (Malignant teratoma intermediate) WHO = teratocarcinoma

EXTRA-EMBRYONIC DIFFERENTIATION → Yolk sac; MTT (Malignant teratoma trophoblastic) WHO = choriocarcinoma

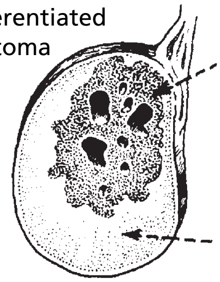
NO DIFFERENTIATION → MTU (Malignant teratoma undifferentiated) WHO = embryonal carcinoma

→ INCREASING MALIGNANCY →

TUMOURS OF THE TESTIS

Malignant teratoma (*continued*)

These tumours, unlike seminoma, are usually irregular in shape and show focal haemorrhage and necrosis: in the better differentiated tumours small cysts are common.

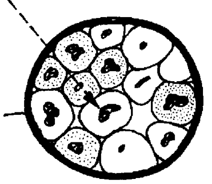


1. **MTD** – In this tumour organoid differentiation is easily recognisable (e.g. formation of intestinal glands, squamous epithelium, cartilage, etc.). It is very rare and although apparently histologically benign, metastases may occur.
2. **MTI** – In addition to mature organised tissue this tumour contains varying amounts of clearly malignant tissue (i.e. MTD + MTU)
3. **MTU** – These tumours are entirely undifferentiated.
4. **Yolk sac and Trophoblastic elements** occur commonly in malignant teratomas: pure forms are rare. α-Fetoprotein (from yolk sac elements) and chorionic gonadotrophin (from trophoblastic elements) are used in diagnosis and monitoring progress.
5. **Combined Germ-Cell Tumours** – Between 10 and 15% of germ-cell tumours consist of a mixture of seminomatous and teratomatous elements.

Spread
The usual mode of spread is by lymphatics to para-aortic lymph nodes. Vascular invasion with lung metastases also occurs.

Prognosis
Modern therapy has greatly improved the overall prognosis.

Intratubular germ cell neoplasia
There is an 'in situ' form of germ cell tumour, often found in association with the malignant tumours described above and represents a precursor form.



MISCELLANEOUS TUMOURS
The following tumours are rare: Sertoli tumours,
Leydig cell tumours,
Lymphoma.

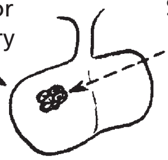
It should be remembered that leukaemia often involves the testes (p.438).

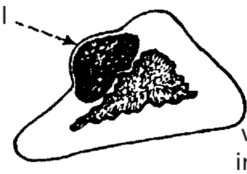
Rarely paratesticular sarcomas occur, e.g. rhabdomyosarcoma in children.

INFERTILITY

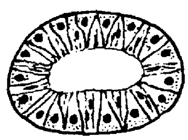
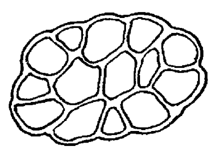
There are numerous causes which affect females or males. The causes are classified as follows:

1. **Pregonadal** – usually endocrine disorders of pituitary or adrenal origin.



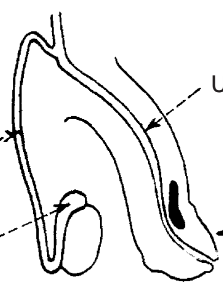


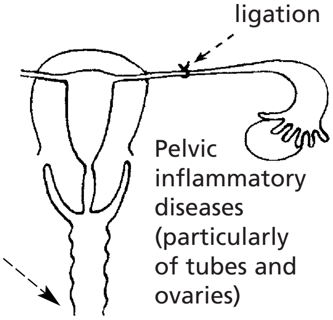
2. **Gonadal** — failure of production of gametes.

	Male	Female
(i) *Chromosomal defects*	**Klinefelter's syndrome** XXY	**Turner's syndrome** XO Gonadal dysgenesis – ovaries represented by small slender functionless tissue – '**Streak gonads**'
(ii) *Germ cell aplasia*	 Tubules lined only by Sertoli cells: – spermatocyte arrest, – often maldescent.	Polycystic ovary syndrome (Stein–Leventhal syndrome)  Ovarian tissue replaced by multiple cysts.

(iii) *Iatrogenic causes:* **Irradiation, chemotherapy,** hormones, e.g. the 'pill' and oestrogens in treatment of prostatic carcinoma.

3. **Postgonadal** – obstruction of passage of gametes.





Note: In some cases of infertility no cause can be detected.

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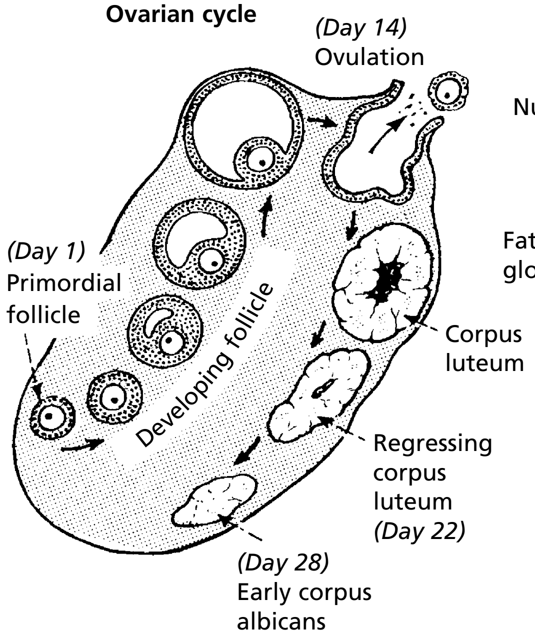
CHAPTER 13

FEMALE GENITAL SYSTEM AND BREAST

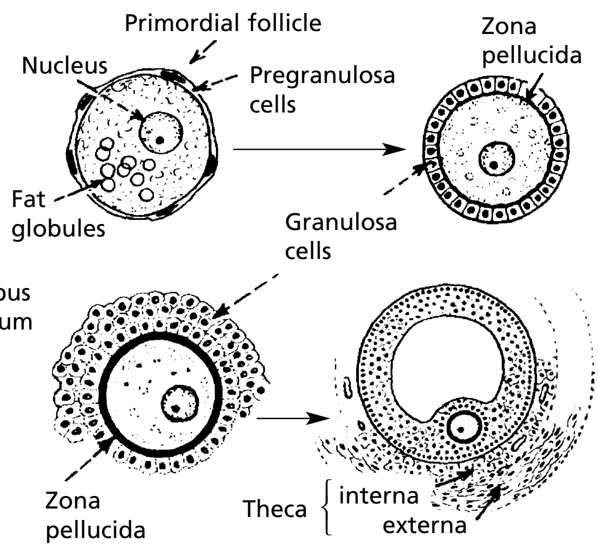
FEMALE GENITAL TRACT – ANATOMY AND PHYSIOLOGY

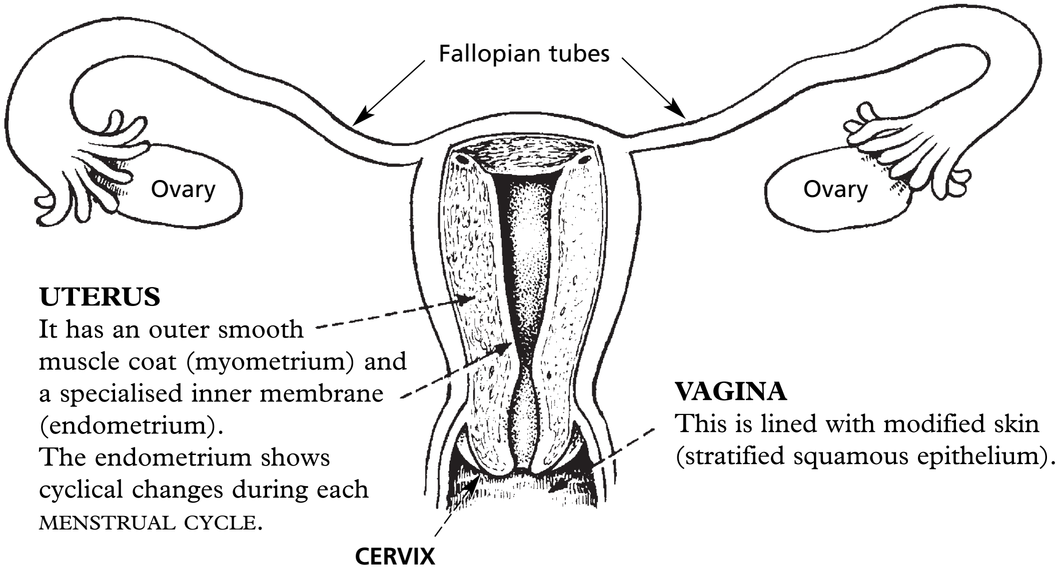
The following diagrams summarise normal anatomy and physiology:

Ovarian cycle



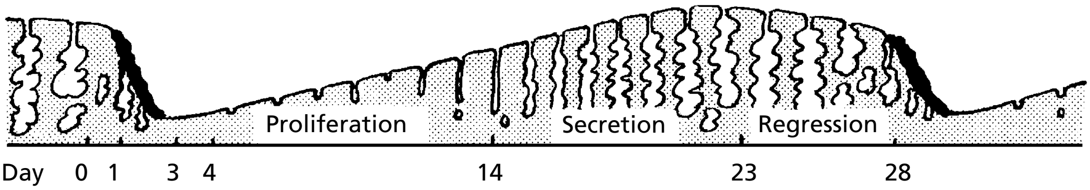
Follicular development



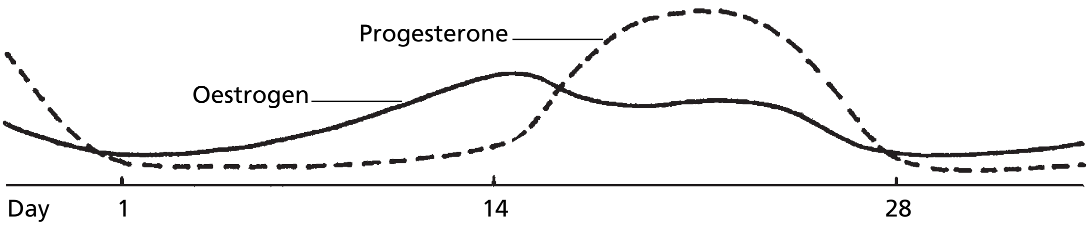


CYCLICAL ENDOMETRIAL CHANGES

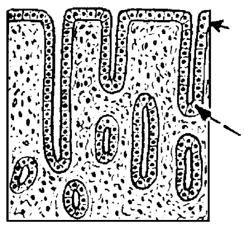
Menstruation



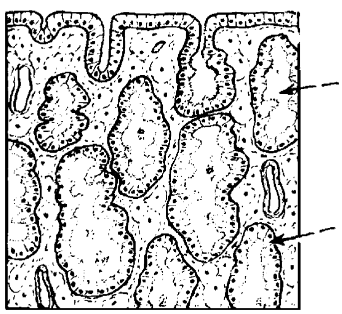
ASSOCIATED OVARIAN STEROID SECRETION



Proliferative phase
This is induced by oestrogen produced by developing ovarian follicles, stimulated by FSH from the pituitary.



Secretory phase
Progesterone produced by the corpus luteum stimulates secretion by the glands. Oestrogen is also produced. The stromal cells enlarge (pseudo-decidual change), oedema is present and vascularity greatly increased.



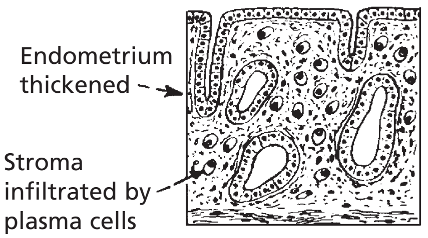
Premenstrual phase
Endometrial growth ceases 5–6 days before menstruation. Prior to menstruation, it shrinks due to decreased blood flow and discharge of secretion. This increases the tortuosity of glands and blood vessels. Finally, apoptosis occurs and the endometrium is shed.

DISEASES OF THE ENDOMETRIUM

Endometritis is now unusual.

Acute infection is nearly always associated with childbirth and abortion – often related to retention of products of conception. Historically, criminal abortion in non-sterile conditions led to severe infection. Gonococcal infection does not commonly extend beyond the cervix but can lead to acute endometritis. Chlamydia may cause acute or chronic endometritis.

Chronic endometritis
This can be seen in chronic pelvic inflammatory disease and in relation to retained products of conception.



Tuberculous endometritis
This is now uncommon in UK. It is the result of infection spreading from the fallopian tubes. If the patient is still menstruating, the tubercles are shed each month: diagnostic biopsy should be done as late in the cycle as possible to allow new tubercles to develop. In some cases, menstruation ceases and caseation occurs.

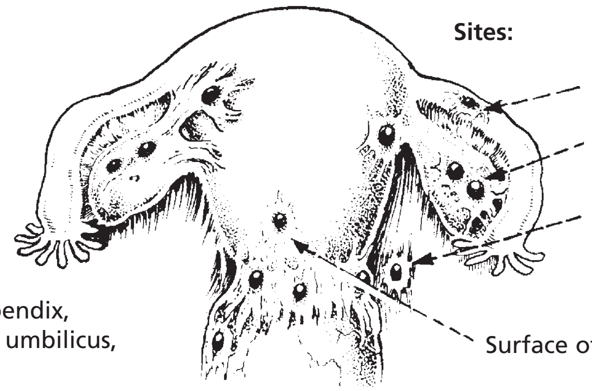
Intrauterine anti-fertility devices
A mild chronic inflammation may be associated with the use of these devices. There may be focal atrophy with mild plasma cell infiltration. Irregular bleeding may result.

DISEASES OF THE ENDOMETRIUM

ENDOMETRIOSIS

This consists of deposits of endometrium outside the uterine cavity.

In most cases, the disease is confined to the pelvis and the genital tract.



Other sites: Caecum and appendix, bladder, rectum, umbilicus, laparotomy scar.

These deposits show cyclical changes. The result is haemorrhage into the local tissues at the time of menstruation. Adhesions develop, often leading to infertility. Malignant change to endometrioid adenocarcinoma occurs uncommonly.

Aetiology

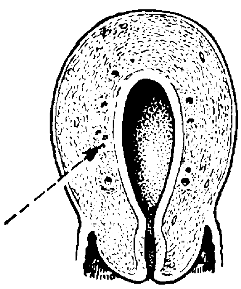
Three theories have been proposed.

1. Retrograde spill of menstrual debris – perhaps the most favoured.
2. Metaplasia of tissues into Müllerian duct elements.
3. Lymphatic and blood borne emboli of endometrial tissue.

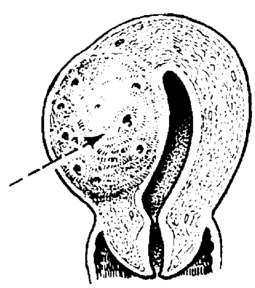
ADENOMYOSIS

Deep down growths of endometrium occur within the myometrium. There is an accompanying overgrowth of muscle and connective tissue. Two macroscopic forms occur:

1. **Diffuse**
   Deposits are confined to inner part of myometrium.
   Foci of endometrium often brownish in colour



2. **Localised**
   Resembling fibroid but with brownish foci



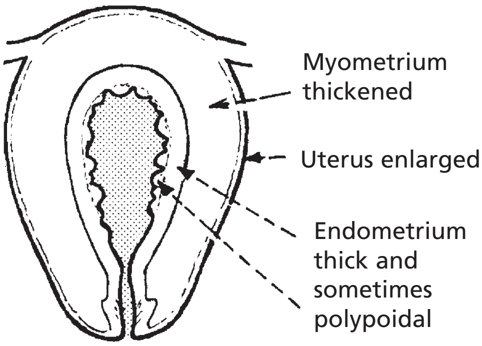
The endometrial deposits communicate with the uterine cavity, but despite this they often contain altered blood in the glands which become cystic. The diffuse type is commoner. Adenomyosis is not related to endometriosis.

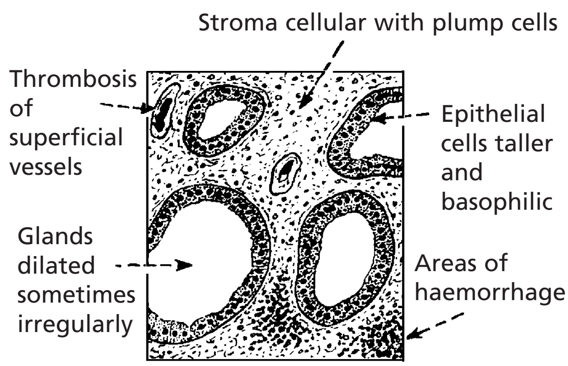
ENDOMETRIAL HYPERPLASIA

Endometrial hyperplasia occurs in 3 forms: Simple hyperplasia, complex hyperplasia and atypical hyperplasia. Of these, atypical hyperplasia is most important as it is associated with an increased risk of malignancy. Progressive molecular genetic alterations occur on the pathway to cancer.

SIMPLE HYPERPLASIA

This tends to occur in the peri-menopausal period. It is due to excess oestrogen stimulation – particularly associated with **anovulatory** cycles, but rarely with oestrogen therapy or oestrogen-secreting tumours.





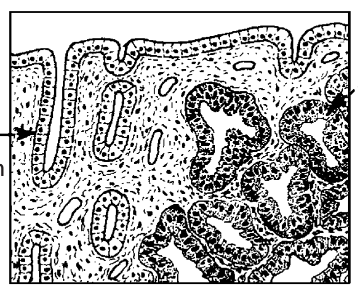
Clinically, there is irregular, frequent and heavy bleeding.

COMPLEX HYPERPLASIA

In this form, hyperplasia is often focal and glands but not stroma are affected. Thus the glands appear crowded, but show no atypia. There is no increased risk of malignancy.

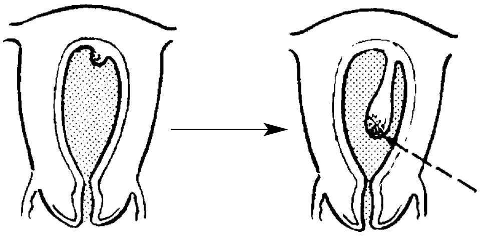
ATYPICAL HYPERPLASIA

In this condition the hyperplasia is focal and cytological atypia with mitotic figures is common. Intervening endometrium may show simple hyperplasia. The importance of atypical hyperplasia is its relationship to the development of adenocarcinoma, i.e. it is considered to be pre-cancerous. Up to 40% have co-existing carcinoma in hysterectomy specimens.



ENDOMETRIAL POLYP

This is a localised proliferation of endometrial glands which becomes pedunculated.

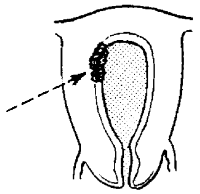


Sometimes polyps are associated with general endometrial hyperplasia. Progressive elongation of the pedicle may lead to venous congestion and bleeding.

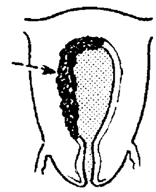
ENDOMETRIAL CARCINOMA

This common gynaecological cancer particularly affects postmenopausal patients, who typically present with vaginal bleeding.

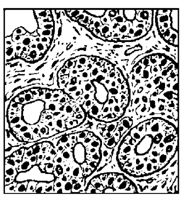
CARCINOMA
This growth may form a *localised* plaque or polyp.



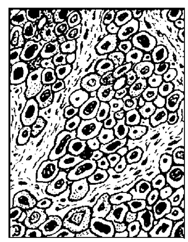
In some cases it appears as a *diffuse* change involving much of the endometrium. It grows initially within the endometrial layer, bulging into the uterine cavity.



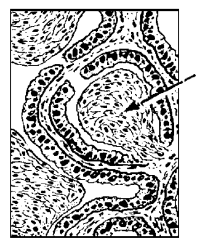
Most growths are well-differentiated adenocarcinomas (endometrioid). These are graded from I – III



GRADE I



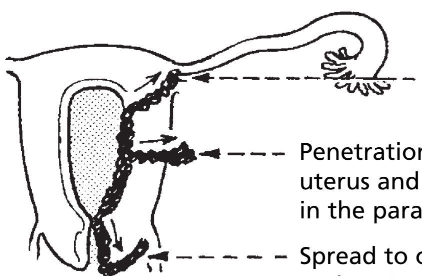
GRADE III

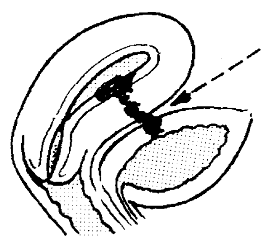


Areas of squamous metaplasia are relatively common; they have no prognostic implication

In some cases with a particularly poor prognosis malignant squamous epithelium is admixed with the adenocarcinoma – so-called ADENOSQUAMOUS carcinoma.
The endometrium possesses no lymphatics and invasion of the myometrium takes place slowly.

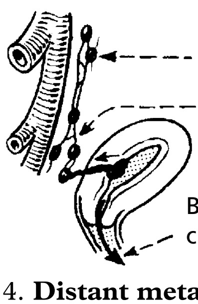
Local extension: this may take place in several directions.





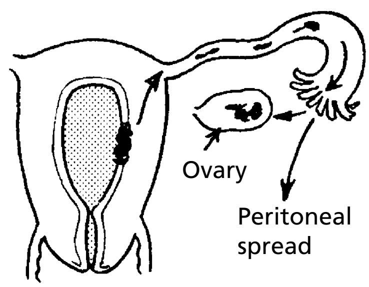
Metastases

1. **Via lymphatics**



2. **Via blood vessels**
Secondary deposits in the vagina and ovaries may be due to this mode of spread

3. **Via fallopian tube**



4. **Distant metastases.** At a late date, secondaries may appear in the liver, lungs and bones. These may be the result of lymphatic or blood spread.

The most important prognostic factor is the stage of the tumour, usually expressed in the FIGO (International Federation of Gynaecology and Obstetrics system).

ENDOMETRIAL CARCINOMA

Aetiology
Endometrial carcinoma is uncommon before the 5th decade. The most important factor is prolonged OESTROGENIC stimulation due to:

(a) endogenous overproduction, e.g. in cases of oestrogen-secreting ovarian tumours.
(b) exogenous oestrogen therapy.
(c) in OBESITY: increased conversion of androstenedione (from adrenals) to oestrone.

ATYPICAL HYPERPLASIA is an important precancerous stage.

Other endometrial malignancies:

ENDOMETRIAL STROMAL SARCOMAS
These rare tumours may be of low grade or high grade.

Low grade tumours – infiltrate extensively through the lymphatics of the myometrium. The cells are cytologically bland and mitoses are few. About one fifth of patients eventually die from the disease.

High grade stromal sarcomas – are highly malignant spindle celled tumours, with poor prognosis. It may be difficult to separate these from uterine leiomyosarcomas.

CARCINO-SARCOMA (Malignant Mixed Müllerian Tumours)
These uncommon tumours have features both of endometrial carcinoma and sarcoma. They often present as soft fleshy masses protruding through the cervix into the vagina.

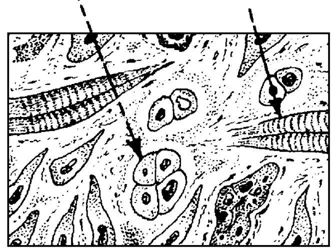
The tumour contains carcinoma and sarcomatous elements.



If these resemble endometrial stroma, the tumour is described as

HOMOLOGOUS

Sometimes stromal elements include malignant cartilage; sometimes striated muscle.



The tumour is then described as

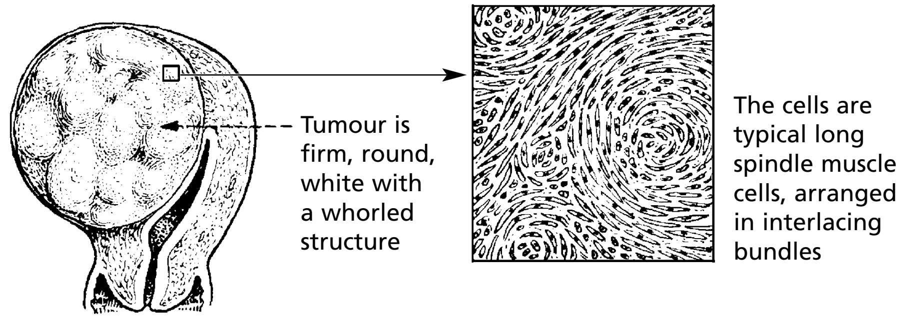
HETEROLOGOUS

DISEASES OF THE MYOMETRIUM

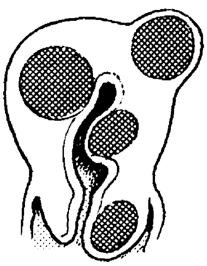
Tumours of the myometrium are extremely common.

LEIOMYOMA (fibroid)

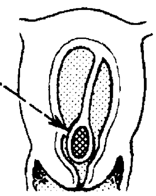
This is a circumscribed growth derived from uterine muscle.



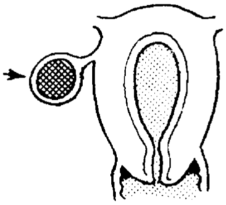
They vary in size from tiny (mm) growths to several cm in diameter and are frequently multiple.
Fibroids may be found in any part of the uterus.



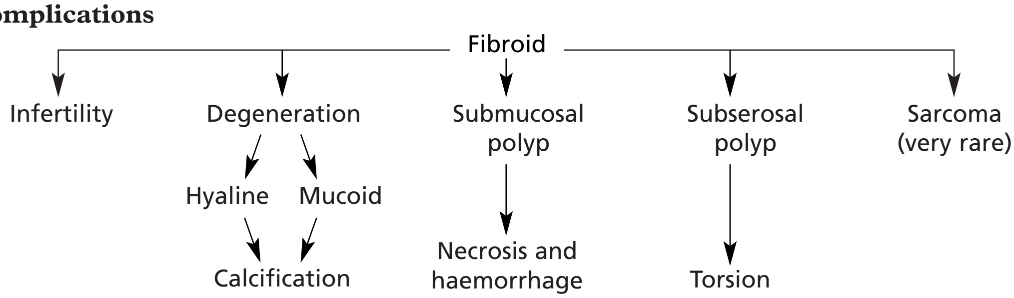
Tumours beneath the endometrium tend to bulge into the cavity and may eventually develop to form a fibroid polyp.



Similarly subserosal polyps may form



Complications



Leiomyoma is one of the commonest tumours, occurring in 15–20% of women over the age of 35. Growth ceases at the menopause.

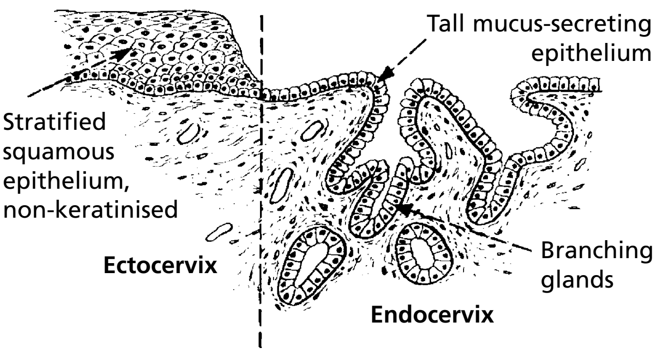
LEIOMYOSARCOMA

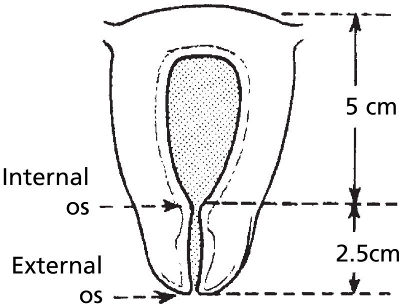
This is a rare tumour which may arise from a preceding leiomyoma, but usually does not. Some tumours are highly malignant but in others with few mitotic figures it is difficult to predict the outcome – these are known as Smooth Muscle Tumours of Uncertain Malignant Potential (STUMP).

DISEASES OF THE CERVIX

The cervix constitutes the lower one third of the uterine body.

It is in two parts: endocervical and ectocervical with different lining epithelium.





The remainder of the cervical wall consists of circular smooth muscle lying in abundant fibroelastic tissue.

At the internal os, the structure gradually merges with that of the uterus proper, the branching glands giving place to the simple tubules of the endometrium, and the proportion of muscle increases greatly.

CERVICITIS

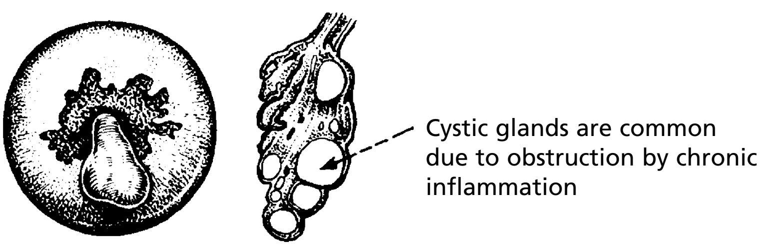
Inflammation of the cervix may be acute or chronic. Acute cervicitis may be due to gonorrhoea or follow cervical laceration at childbirth.

Chronic cervicitis is commoner and may be due to candida, trichomonas (p.506) and chlamydia. The last is associated with reactive lymphoid follicles (follicular cervicitis).

Viral infections of the cervix include Herpes Simplex Virus (Type II) and human papilloma viruses (HPV). The latter can cause simple viral warts or be associated with cervical intraepithelial dysplasia and neoplasia (CIN) and invasive carcinoma (p.504).

CERVICAL POLYP

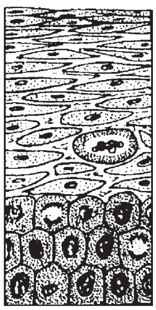
This is a local proliferation of endocervical mucosa which becomes pedunculated and may protrude through the cervix.



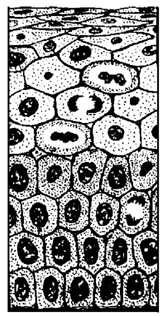
CERVICAL INTRAEPITHELIAL NEOPLASIA (CIN)

The transformation zone
From puberty onwards and particularly in pregnancy the squamo-columnar junction presents on the vaginal surface of the external os. This is the area where **squamous metaplasia** occurs. It is important because cervical squamous carcinoma and its precursor **cervical intraepithelial neoplasia** (CIN) begin there. Within this metaplastic epithelium, **dysplastic** changes may develop. They are graded as CIN I, II and III. Later, in some cases, invasive squamous carcinoma develops.

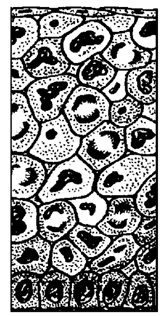
CIN I = Mild dysplasia.



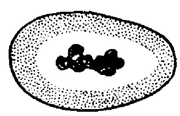
CIN II = Moderate dysplasia



CIN III = Severe dysplasia and Carcinoma in situ.

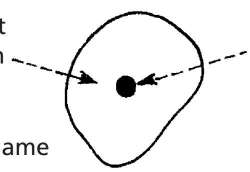


Koilocytes (cells with a wrinkled pyknotic nucleus and perinuclear cytoplasmic clearing) are often seen in the suprabasal layers and indicate HPV infection.

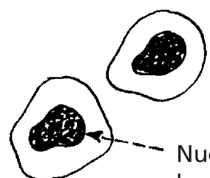


CYTOLOGY and CIN
The cervical screening programme aims to detect CIN and thus prevent the development of invasive carcinoma. Cellular preparations from the squamo-columnar junction obtained by a cervical brush are stained by Papanicolaou's method (liquid-based cytology). The cells can be examined for dysplasia – so-called dyskaryosis. Inflammatory changes, e.g. due to candida infection, may be seen.

Normal smear



Dyskaryosis



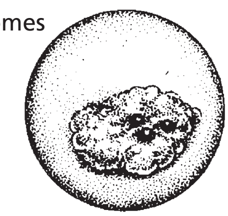
The cytology is a SCREENING TEST. Patients with abnormalities are referred for colposcopy where abnormal epithelium turns white on exposure to acetic acid (acetowhite). Punch biopsy to diagnose dysplasia is followed by laser ablation (laser loop excision of transformation zone). New techniques to identify proliferating and malignant cells are being rapidly developed.

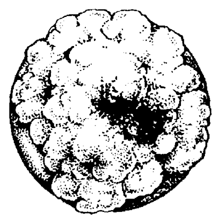
CARCINOMA OF CERVIX

CARCINOMA

This is the most common malignant tumour of the female genital tract, even where there is a vigorous screening campaign for early diagnosis and eradication of dysplasia. The tumour is a squamous carcinoma in 90% of cases, and an adenocarcinoma in 10%. Most squamous carcinomas arise at the squamo-columnar junction: most adenocarcinomas arise within the endocervical canal.

The cervix becomes indurated with necrosis and ulceration.





Later, a large fungating mass is produced.

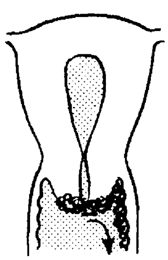
Microinvasive carcinoma is the earliest stage of invasive cancer – where spread is less than 5 mm in depth. This is associated with an excellent prognosis.

Spread

Until a very late stage, the disease is confined to the pelvic cavity. The patient commonly dies before distant metastases appear.

Local spread takes place in several directions:

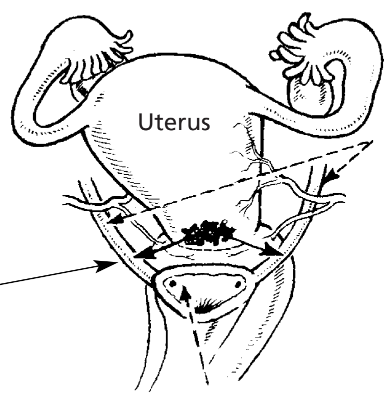
1. **Downward extension.**



(a) The growth encircles the external os. In some cases it causes obstruction of the cervical canal and pyometra may develop.

(b) Direct extension to the vagina follows.

2. **Lateral extension.** The anatomy of this region is important.

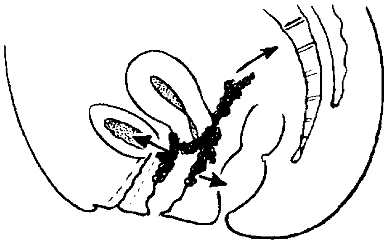


The ureters come very close to the cervix in their travel to the bladder, and are often involved in extension of the tumour to the parametrium. The ureters may be obstructed by pressure or invasion. Renal infection and failure follow.

CARCINOMA OF CERVIX

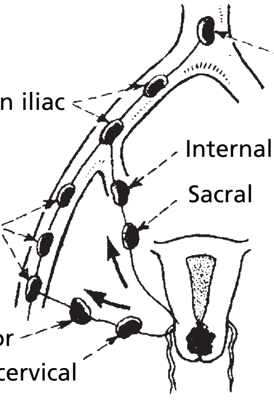
Spread of carcinoma (*continued*)

3. **Anterior and posterior extension**



Direct invasion of the bladder or rectum results in fistulous communications. Spread along the uterosacral ligaments involves the sacral nerves, causing intractable pain.

4. **Lymphatic spread**
   This occurs early and involves the chains of lymph nodes in the pelvis.



Prognosis

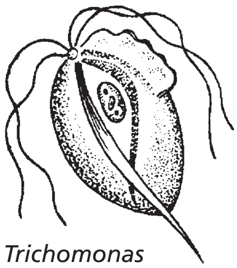
With modern treatment there is an 80% 5-year cure rate when the disease is diagnosed early, i.e. confined to the cervix: it falls significantly if spread to the pelvis has occurred.

Previously death was commonly due to a combination of renal failure and sepsis: fatal haemorrhage from eroded vessels also occurred. With better local control death is usually due to metastases.

Aetiology

Cervical cancer is caused by infection with strains of human papilloma virus, a sexually transmitted disease. For this reason vaccination against HPV is now offered to girls of secondary school age.

DISEASES OF VAGINA AND VULVA



Trichomonas vaginalis

Vaginal discharge is a common complaint especially in parous women. In many cases it is related to chronic cervicitis. There are however a number of inflammatory conditions which arise primarily in the vagina.

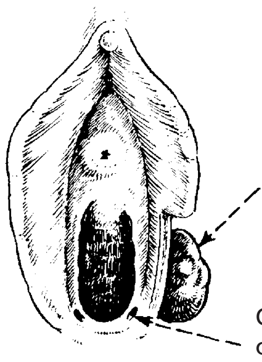
Gonococcal infection may produce an acute inflammation with purulent discharge but it is often asymptomatic.

Purulent discharge is also associated with infection by a protozoon, *Trichomonas vaginalis*. The discharge tends to be frothy. It is commonly transmitted during sexual intercourse. The male can also be infected.

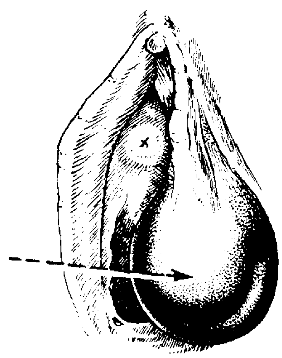
Candida albicans infection is common in pregnancy, in diabetes and in patients undergoing antibiotic or immunosuppressive therapy.

PRIMARY TUMOURS of the VAGINA are rare. Squamous carcinoma occurs in the upper vagina of women and may lead to fistula formation between the vagina and the bladder or rectum. Vaginal intraepithelial neoplasia (VAIN) may be associated with CIN and VIN. Historically, clear cell carcinoma was sometimes found in adolescent girls, due to the effect on the fetus of administration of diethylstilbestrol to the patient's mother during early pregnancy. It arose in a background of vaginal adenosis – a proliferation of glands within the vaginal wall.

VULVAL INFLAMMATION is common in post-menopausal women. It is related to atrophy of the skin, which has very thin epithelial covering at this phase of life and is easily abraded. Inflammation at other periods of life frequently involves Bartholin's gland.



The duct may become blocked with cyst formation. This may become infected – Bartholin's abscess.



Two conditions which mainly occur in the tropics and are seen only very occasionally in temperate countries are:

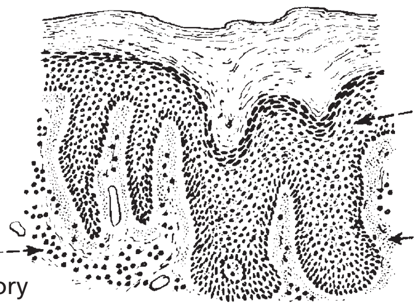
1. **Lymphogranuloma venereum.** This is a chlamydial infection which starts as an ulcer on the vulva or in the vagina. It heals in a short time, only to be followed by a chronic suppurative reaction in the inguinal and sometimes pelvic lymph nodes. This leads to extensive scarring and sometimes fistulous openings in the pelvic viscera.
2. **Granuloma inguinale.** This begins as a papule on the vulva, perineum or vagina. It ulcerates and can spread widely, causing extensive destruction of tissue. Histologically, it is a granuloma and the infecting organism (*Calymmatobacterium granulomatis*) can be seen in macrophages.

DISEASES OF VAGINA AND VULVA

LEUKOPLAKIA AND PREMALIGNANCY

Leukoplakia is a descriptive term meaning white patches. These are common on the vulval and perineal region in almost any chronic inflammatory skin condition due to the local moist conditions, e.g. chronic dermatitis (lichen simplex), fungal infection and lichen sclerosis.

Vulval intraepithelial neoplasia (VIN) presents as white patches which show varying degrees of dysplasia. It is premalignant.



The degree of dysplasia varies, amounting to carcinoma in situ in some cases.

These changes are now numerically graded VIN I, II and III, i.e. Vulvar Intraepithelial Neoplasia (analogous to CIN).

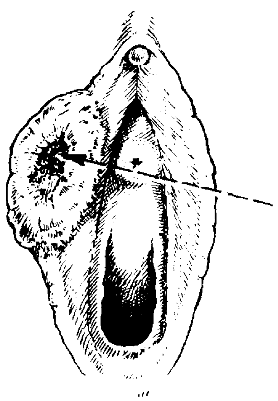
TUMOURS OF THE VULVA

Benign tumours are common. CONDYLOMATA ACUMINATA are papillomas due to infection by Human Papilloma Virus (HPV) types 6 or 11. Koilocytosis (see p.503) in the superficial keratinocytes is characteristic.

Sweat gland tumours (hidradenomas) may also occur.

Carcinoma of vulva

This is a rare condition found usually in women in the 6th and 7th decades of life.



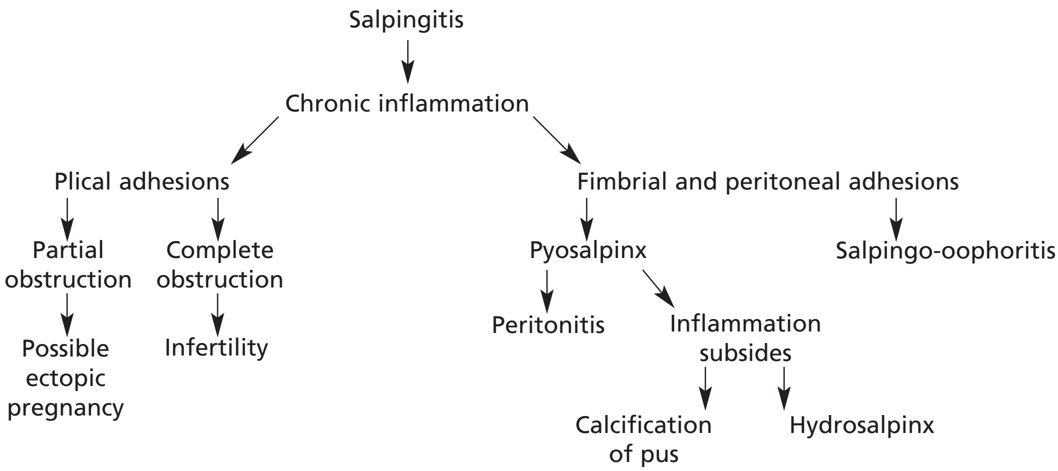
The inguinal glands on both sides are invaded at an early stage. The tumour is usually a squamous carcinoma.

DISEASES OF THE FALLOPIAN TUBE

Acute Salpingitis
This is the result of ascending infection from the endometrium: some cases follow abortion and puerperal infection. Chlamydia may cause acute salpingitis.

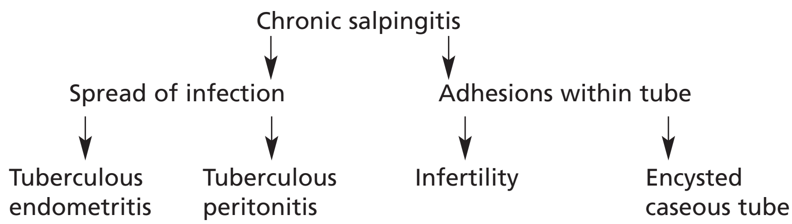
The inflammation is usually bilateral and primarily involves the tubal plicae which are congested and oedematous; with a purulent exudate.

If resolution of the acute inflammation does not occur (antibiotic therapy is important) chronic salpingitis follows. The term 'pelvic inflammatory disease' is used.



Tuberculous salpingitis
Tuberculous infection of the female genital tract, for some unexplained reason, almost always starts in the fallopian tube. It is usually due to blood spread from some other site: only very occasionally it is secondary to tuberculous peritonitis.

The complications are those expected of a chronic salpingitis with the added element of caseation.

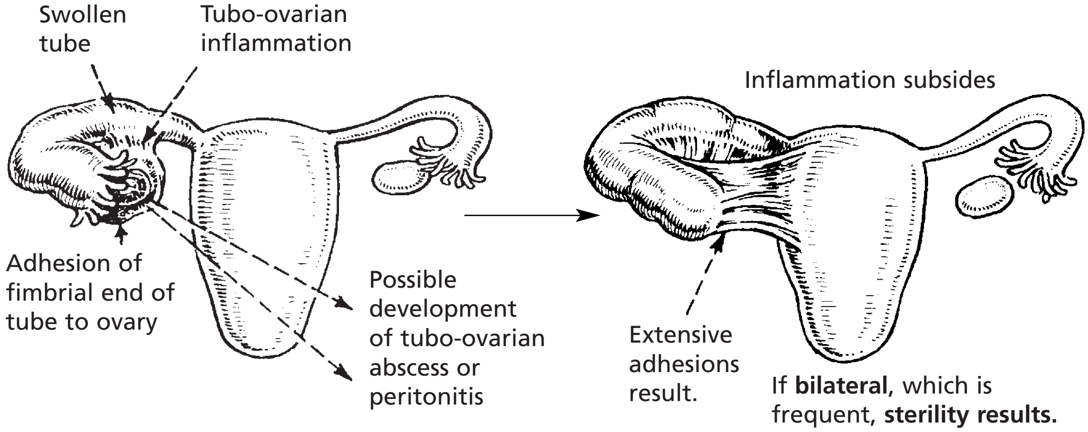


Tumours of the fallopian tube
Benign tumours such as fibroma and myoma occasionally occur. Small cysts of congenital origin are common around the fimbrial ends of the tubes.

Carcinoma, usually a papillary adenocarcinoma, is extremely rare. There may be a profuse watery secretion which appears as a vaginal discharge. There is an association with BRCA mutations.

DISEASES OF THE OVARIES

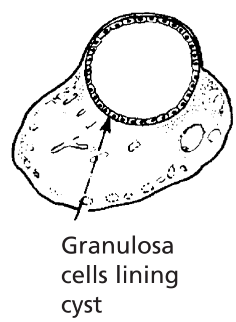
Oophoritis
Inflammation of the ovaries is always secondary to disease of the fallopian tubes or peritoneum. The inflamed fimbrial end of the tube becomes adherent to the ovary and direct spread of infection occurs. Tubo-ovarian inflammation is also associated with the presence of an intra-uterine contraceptive device (see p.496). Important local complications may follow.



The ovary may be similarly involved in tuberculous salpingitis, and caseating lesions can occur.

Ovarian changes of functional origin
The control mechanisms of ovarian function frequently develop faults resulting in abnormalities of structure:

Follicular cysts
These may be single or multiple. The maximum diameter of a normal Graafian follicle is 1.5–2 cm. Single follicular cysts may be several centimetres in diameter.

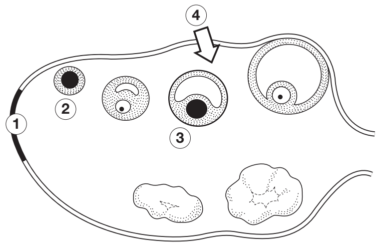


Bilateral, multiple small cysts of this nature occur in polycystic ovarian disease and are associated with obesity, hirsutism and oligomenorrhoea (Stein–Leventhal syndrome, polycystic ovary syndrome).

Theca lutein cysts
These are cysts from which the granulosa cells have disappeared, leaving cysts surrounded by luteinised thecal tissue.

DISEASES OF THE OVARIES

Many types of ovarian tumours exist. Various classifications have been suggested; none is completely satisfactory. The following is a simple working classification:



1 Epithelial tumours (derived from surface epithelium)
2 Germ cell tumours
3 Sex cord/stromal tumours
4 Secondary (metastic) tumours

COMMON EPITHELIAL TUMOURS

These comprise 70% of all ovarian tumours and 90% of malignant tumours and are found in adult life, very rarely in children.

Histogenesis: The ovarian surface epithelium and the various mature Müllerian structures have a common origin in EMBRYONAL COELOMIC epithelium. The ovarian surface epithelial stem cells retain the ability to differentiate along different pathways: this explains the histological appearance of these tumours.

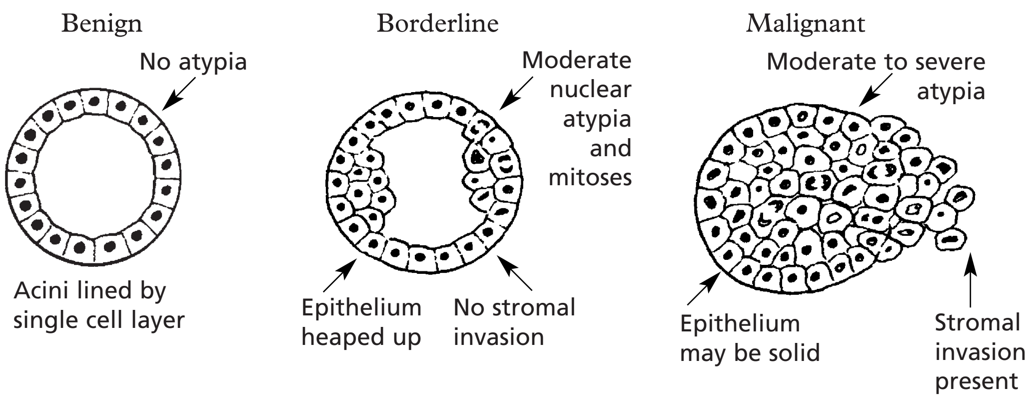
EMBRYONAL COELOMIC EPITHELIUM → MATURE OVARIAN SURFACE EPITHELIUM

↓ ↓

Mature Müllerian tissues → ***analogous TUMOURS***

e.g.
1. Tubal epithelium → SEROUS
2. Endocervical epithelium → MUCINOUS
3. Endometrial epithelium → ENDOMETROID
4. Transitional epithelium → BRENNER

The histological features relate to a spectrum of behaviour:



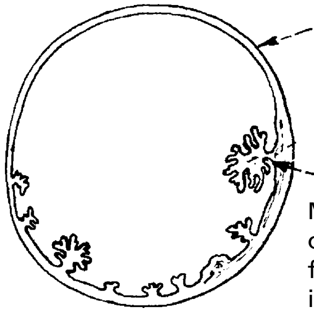
Prognosis: Excellent (100%) | Usually good (90% at 5 years) | Poor (10–20% at 5 years)

COMMON EPITHELIAL OVARIAN TUMOURS

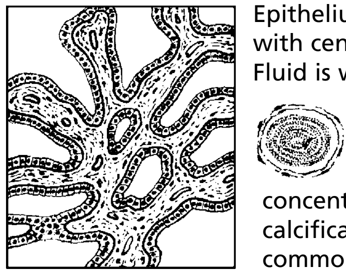
1. SEROUS TUMOURS

(a) Serous cystadenoma

Twenty-five per cent of all ovarian tumours are of this variety. In a third of cases they are bilateral, but they almost never reach the large size of the mucinous tumours.



Some tumours have small loculi with papillary formations making them appear solid.

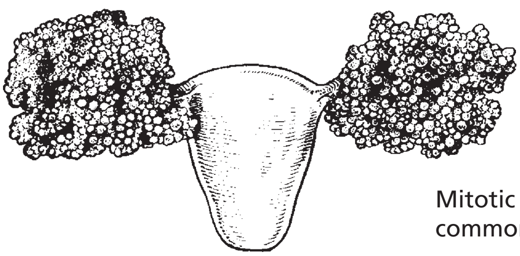


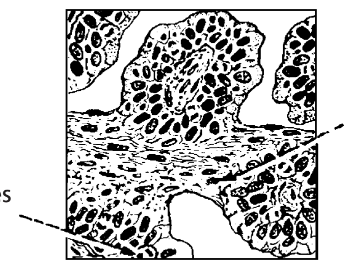
Complications

1. Torsion may occur
2. Malignant transformation is common and 30% of malignant tumours are bilateral.

(b) Papillary (serous) cystadenocarcinoma

This is the commonest malignant tumour of the ovary – responsible for 40% of the total. Usually it takes the form of exuberant papillomatous growths extending over the surface and obliterating the ovarian structure. It is often bilateral.

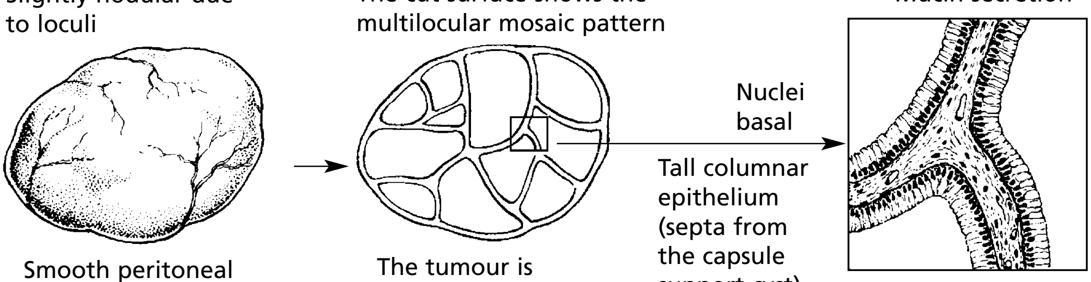




2. MUCINOUS TUMOURS

(a) Mucinous cystadenoma

This accounts for 20% of all ovarian tumours. It can reach a very large size and is typically multilocular. 25% are bilateral.



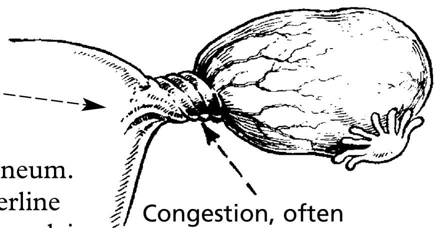
CARCINOMA OF THE OVARY

Complications

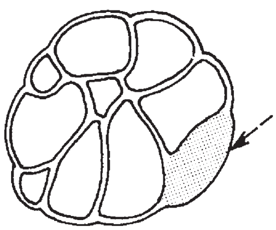
(i) **Torsion of the pedicle.** This is not uncommon with a large ovarian tumour of any type.

(ii) **Rupture.** This may lead to seeding of the mucin-secreting epithelium on the peritoneum.

(iii) **Malignant transformation** including borderline tumours. Cells are large, with large irregular nuclei. Mitoses are common; slight secretion present.



(b) **Mucinous cystadenocarcinoma**



This accounts for 20% of all cases of primary carcinoma of the ovary. It almost always arises as a malignant transformation of a benign cystadenoma.

Areas of solid growth appear in the cyst wall.

Frequently in the malignant areas, florid papillary structures are formed and where the change is widespread it may be difficult to differentiate it from the malignant form of papillary cystadenoma.

3. **ENDOMETRIOID TUMOUR**

In a considerable number of cases, ovarian carcinoma has a solid or semi-solid appearance and as such starts off as a growth smaller than either of the cystic tumours.

Microscopically, these show differentiation towards an endometrial pattern and are termed 'endometrioid'. Some cases arise in endometriosis. Endometrioid adenofibroma is the benign equivalent.

4. **BRENNER TUMOURS**

These are essentially benign and show islands of transitional epithelium in a fibrous stroma.

Progress in ovarian carcinoma

Spread of ovarian cancer in the early stages is by direct extension to the pelvic peritoneum. The papillary serous cancer seeds widely in the peritoneal cavity and only later are lymphatics invaded and metastases appear.

The mucinous variety rarely spreads by lymphatics.

The overall 5-year survival rate for ovarian cancer is only 30% and death often takes place within 2–3 years due to cachexia and interference with intestinal and renal function.

Aetiology

Most cases are sporadic. Nulliparous women with a late menopause have an increased risk. There is a family tendency – especially in women with mutation of the BRCA-1 and BRCA-2 genes.

Tumour marker

CA125 is a glycoprotein: serum levels are raised in about 50% of patients with ovarian carcinoma.

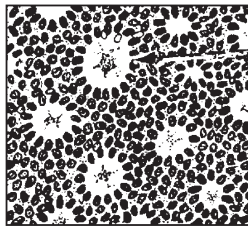
TUMOURS OF THE OVARY – SEX CORD STROMAL

These may be divided into two broad groups:

1. Those tending to produce excess oestrogen: granulosa cell tumours and thecomas.
2. Those producing androgens and virilisation: Sertoli–Leydig cell tumours, hilus cell tumours and lipid cell tumours.

Granulosa cell tumour

This is composed of cells resembling the granulosa cells lining Graafian follicles. They vary in size from a few mm to large cystic structures. Commonly, the smaller varieties are found deep in the ovarian substance. This tumour may be found at any age: 5% occur in children; 50% in the child-bearing years; 40% postmenopausally.



All granulosa cell tumours are potentially malignant – they may recur, sometimes many years after removal.
Measurement of serum **inhibin** (a glycoprotein produced by granulosa cells) is useful in following progress.

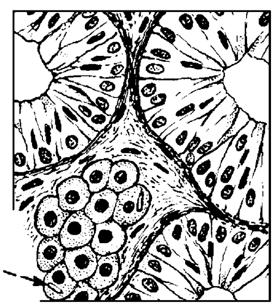
Thecoma

This is a spindle-celled tumour, found mainly during the 3rd, 4th and 5th decades of life. It is benign and rarely recurs.

Function of these tumours varies widely. Oestrogenic effects consist of:
1. Precocious puberty in children.
2. Hyperplasia of endometrium. This may be atypical and carcinoma develops occasionally.

Fibromas are histologically similar but do not produce hormones. They may be associated with pleural effusion (Meig's syndrome).

Sertoli–Leydig cell tumours (androblastoma)



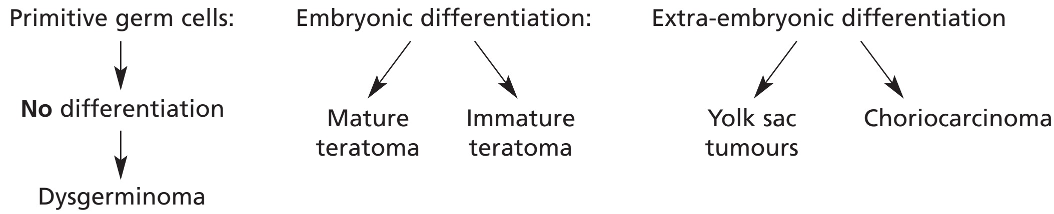
This typifies the virilising tumour group. It is a rare tumour. The degree of virilisation varies. Usually a small yellow tumour within the ovary, it is characteristic on microscopy. Some of these tumours are malignant and consist of poorly differentiated spindle cells with occasional tubule formations.

The androgens, if secreted, result in:
1. Atrophy of breasts and external genitalia
2. Deepening of voice, temporal recession of hair
3. Growth of facial and body hair
4. Enlargement of clitoris.

TUMOURS OF THE OVARY – GERM CELL

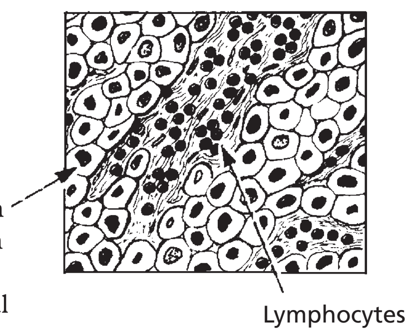
GERM CELL TUMOURS

These arise from primitive germ cells capable of differentiating in many ways. The following diagram indicates the main varieties of tumour produced.



Dysgerminoma

This is a solid tumour, usually ovoid with a smooth capsule, greyish colour and rubbery consistency. Like all germ cell tumours it is commoner in younger age groups. It is sometimes bilateral. Some cases are found in association with gonadal dysgenesis.



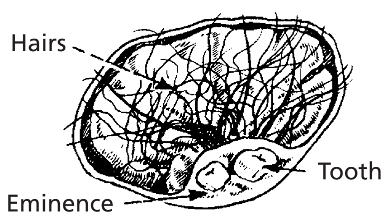
Microscopically, it consists of large clear round cells with large nuclei resembling germ cells. These are arranged in alveoli separated by fine connective tissue infiltrated by lymphocytes. These histological appearances are identical to those of seminoma of the testis.

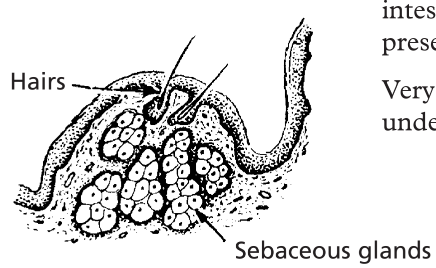
Dysgerminomas are malignant tumours spreading to para-aortic lymph nodes. They are radio-sensitive and also respond to chemotherapy.

Teratomas

These are of two main varieties: (1) Mature and (2) Immature.

Mature cystic teratoma (dermoid cyst)





This is one of the commonest ovarian tumours and it occurs at all ages.

It is unilocular with an eminence on one aspect from which hairs grow. Teeth may be present. The cyst is lined by stratified squamous epithelium. Sebaceous glands, nervous tissue, respiratory, intestinal epithelium and thyroid tissue may also be present.

Very occasionally the squamous epithelium may undergo malignant change.

TUMOURS OF THE OVARY – GERM CELL AND SECONDARIES

Teratomas (*continued*)

Immature teratoma
The tumours are predominantly solid and are malignant. They contain immature tissues, typically of primitive nerve tissue and mesenchymal tissue. They may metastasise to the peritoneum where the nerve tissue may differentiate (gliomatosis peritonei).

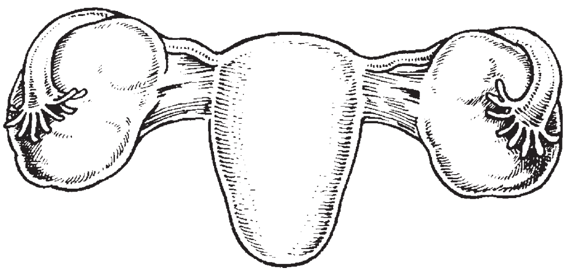
Chemotherapy has greatly improved the prognosis in these cases.

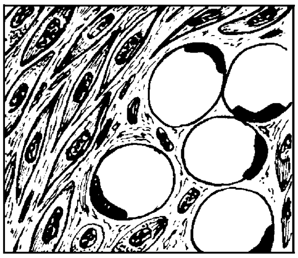
Solid tumours are occasionally seen consisting only of thyroid tissue (struma ovarii) or carcinoid tumour cells.

Extra-embryonic tumours (yolk sac tumours, choriocarcinoma).
These are very rare and highly malignant, but modern chemotherapy has greatly improved the diagnosis.

SECONDARY TUMOURS
The ovaries are often the site of metastases from the breast, lung, intestinal system, etc. They are commonest during the child-bearing years.

Krukenberg tumour
This is a very characteristic secondary tumour due to metastatic deposits from an undiscovered stomach carcinoma in a pre-menopausal woman. Both ovaries are involved. They are firm and fibrous, of equal size, smooth and slightly lobulated. No adhesions are present.





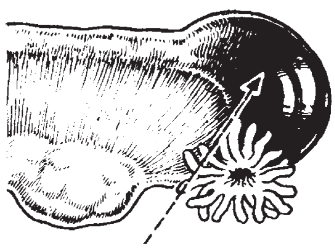
Histologically there are large tumour cells, eccentric nuclei and clear cytoplasm containing mucin (signet ring cells) lying in a spindle-celled stroma.

ECTOPIC PREGNANCY

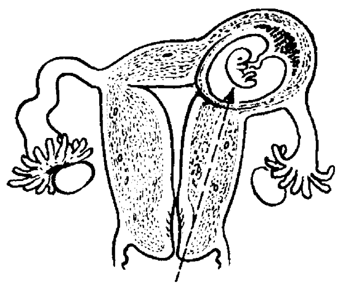
This means implantation of the fertilised ovum outside the uterine cavity usually in the fallopian tube.

Aetiology. Most commonly the tube has been previously damaged by salpingitis, leading to partial blockage of the tube. There has been an increased incidence of ectopic pregnancy in women fitted with intrauterine contraceptive devices.

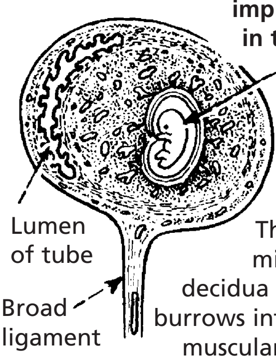
Sites of implantation



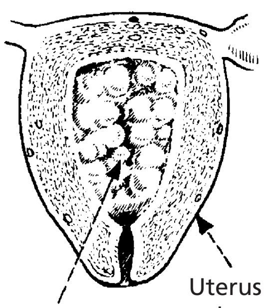
Ampullary implantation
This is the commonest.



Cornual implantation (rare)



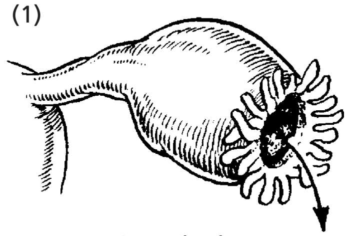
Uterine changes



Erosion of the tubal tissues by the ovum results in **rupture**.

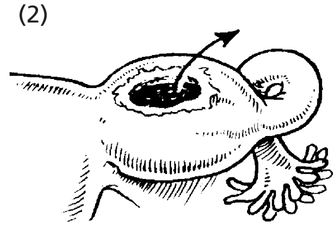
This is the commonest finding.
The direction of rupture varies:

(1)



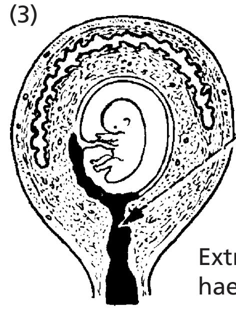
Rupture into the lumen of the tube and leakage into peritoneal cavity.

(2)



Rupture directly into the peritoneal cavity. If the implantation is cornual, there may be a further complication – damage to the uterine arteries with **arterial bleeding.**

(3)



Exceedingly rarely the whole pregnancy – ovum and placental tissue – aborts into the peritoneal cavity where it reimplants. Usually development is limited and the fetus dies, but continuation of the pregnancy almost to term has been reported.

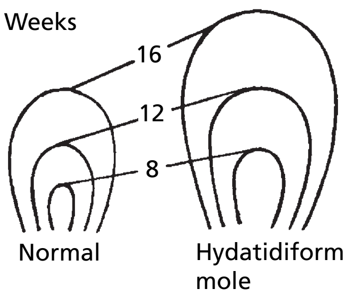
GESTATIONAL TROPHOBLAST DISEASE

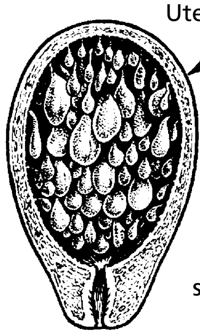
This term describes proliferative conditions of placental tissue.

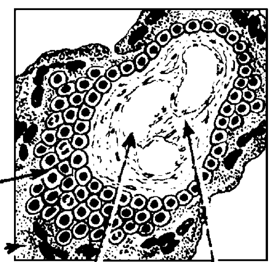
HYDATIDIFORM MOLE

This occurs in two forms:

1. **Complete.** This occurs when an ovum lacking its nucleus is fertilised by one or two sperm. The pregnancy lacks a fetus. The uterus is filled by cysts of varying size.







Blood and urine levels of chorionic gonadotrophin are high.

1a. **Invasive mole.** Villi may penetrate the myometrium and invade blood vessels with pulmonary 'metastases'. There is usually complete regression after hysterectomy however.

Prevalence: Uncommon in the West (1 in 1500 pregnancies) but common in the East (1 in 120 pregnancies).

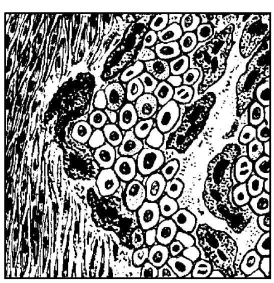
Genetics: Both sets of chromosomes are paternal, usually 46XX.

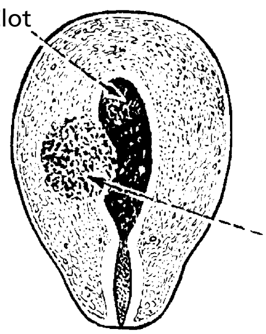
Progress: Abortion is the usual outcome: there is a 2–3% risk of CHORIOCARCINOMA developing.

2. **Partial mole.** This occurs when an ovum is fertilised by two sperm resulting in a triploid karyotype 69XXY or 69XXX. Part of the placenta shows cystic change and a fetus, usually malformed, may be present. While trophoblast may persist there is no risk of choriocarcinoma.

CHORIOCARCINOMA

This is a malignant tumour of trophoblast and is by definition of fetal origin. It usually follows hydatidiform mole. Pleomorphic cytotrophoblast and syncytiotrophoblast, showing numerous mitoses, invade blood vessels causing haemorrhage and early lung metastases either as a single large 'cannon-ball' haemorrhagic mass or multiple small emboli ('snow-storm' lung). The high blood and urine concentrations of chorionic gonadotrophin are used to monitor progress and treatment which is now usually successful.

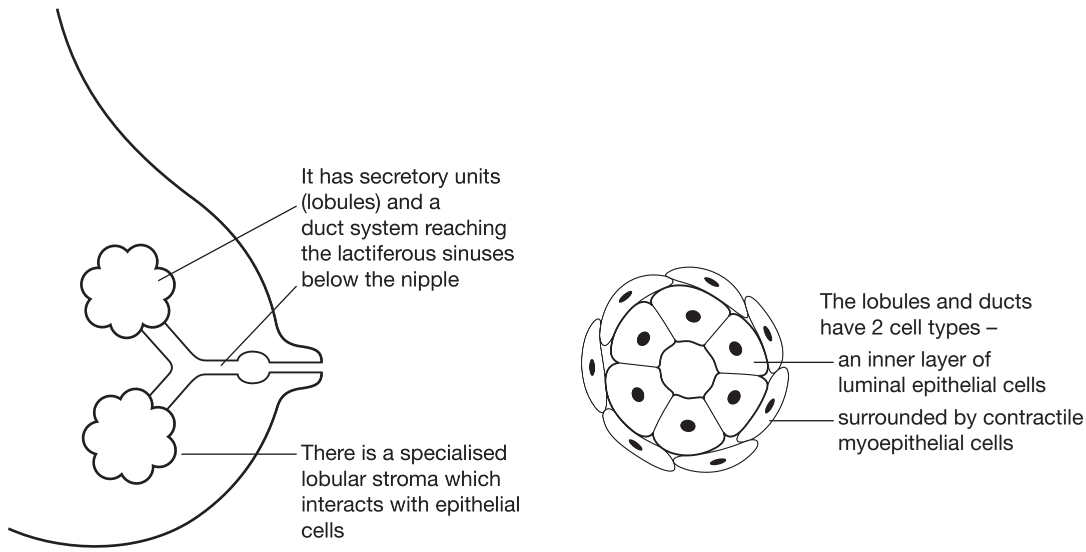




The myometrium is infiltrated by masses of malignant trophoblast and blood vessels are eroded.

BREAST STRUCTURE AND FUNCTION

The breast is a greatly modified sweat gland which has evolved to secrete nourishment to infants.



The breast responds to oestrogen and progesterone both during the menstrual cycle and, especially, during pregnancy in preparation for lactation.

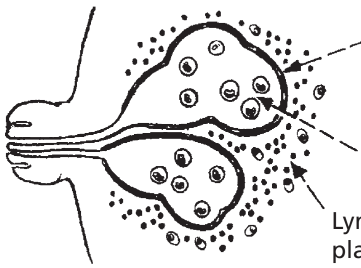
BENIGN DISEASES OF THE BREAST

Acute infection is an occasional complication of **lactation**.

Fissures or abrasions of the nipple allow staphylococci to be transmitted from the baby. Abscesses may form in the breast with scarring.

Chronic infection e.g. tuberculosis is very uncommon.

Duct ectasia (plasma cell mastitis)
This chronic inflammatory reaction is associated with ectasia of the ducts (cystic dilatation).



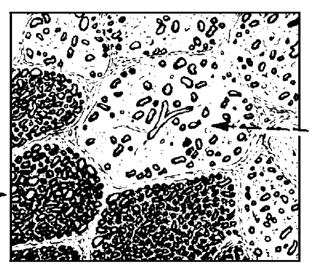
Infection of the dilated ducts allows escape of contents into the tissues resulting in *granulomatous* reaction. Clinically it may raise suspicion of duct carcinoma.

Traumatic Fat Necrosis occurs especially in large pendulous breasts and results in irregular granulomatous fibrosis which may mimic carcinoma.

In some cases of **Silicone Implant**, continuing granulomatous inflammation with fibrosis occurs in the 'capsule' due to leakage of silicone.

Fibrocystic change
This change presents as a lump or lumpiness of the breast in pre-menopausal women.

1. **Fibrosis**. There is progressive hyalinisation of the stroma.
2. **Cyst formation.** Obstruction of ducts leads to dilatation of the ducts and acini. The lining epithelium may show apocrine metaplasia.
3. (a) **Adenosis**. This is an increase in the number of lobules and in the size of existing lobules.

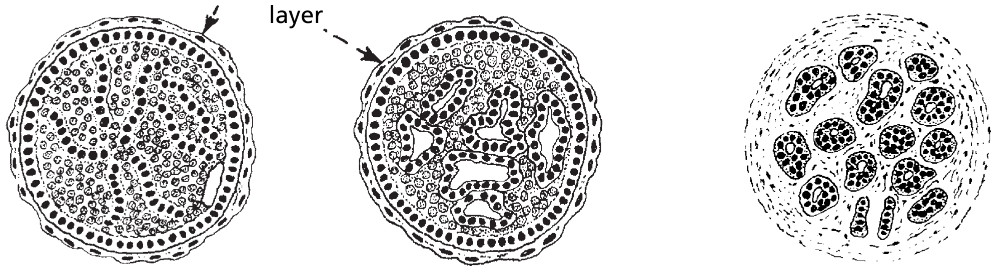


   (b) **Sclerosing adenosis**
   This is a localised condition which may simulate carcinoma. There is proliferation of acini and stroma, and mitotic activity can be marked but there is no danger of malignancy.

BENIGN DISEASES OF THE BREAST

Fibrocystic change (*continued*)

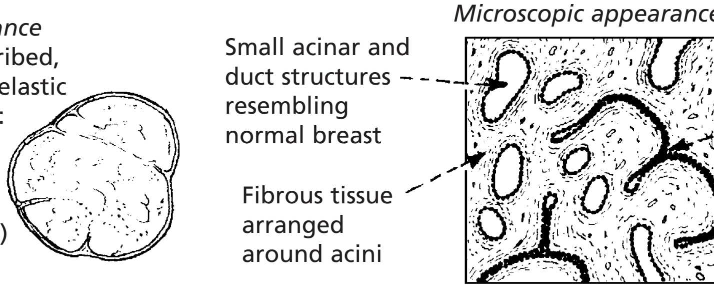
4. **Epithelial hyperplasia** means proliferation of the epithelial component of the breast and is important because some forms lead on to breast cancer.



Fibrocystic change is very common, and the various changes are ascribed to abnormal and exaggerated responses of the breast tissues to the cyclical physiological menstrual hormonal stimuli; they are essentially benign.

Fibroadenoma

This is a benign nodular proliferation, now considered to be a component of fibrocystic change and not a true neoplasm. It is usually single, occurring in young women. It presents clinically as a small, firm, mobile lump.



Radial scar

This small (up to 1 cm diam.), firm lesion shows a central dense fibrous core with radiating fingers of fibrosis entrapping and distorting glandular elements. It is benign but can be confused with carcinoma even on histological examination.

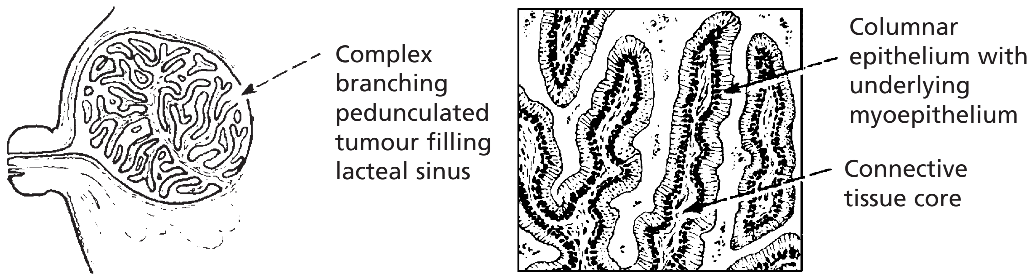
Similar but larger lesions, also detected by mammography, are known as **complex sclerosing lesions**.

BENIGN BREAST TUMOURS AND IN SITU CARCINOMA

Duct papilloma

This tumour may develop in any part of the duct system of the breast, but is most common in the lacteal sinuses at the nipple. Two forms exist:

1. **Solitary papilloma.** These are almost always near the nipple.



Prominent myoepithelium gives a double layer of cells covering the fronds.

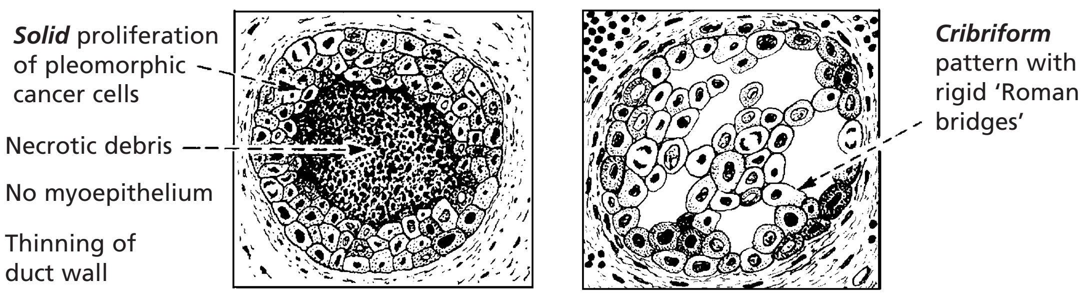
2. **Multiple papillomas**

These may be distributed throughout the duct system. There is a small increased risk of cancer occasionally developing.

In both forms, there may be discharge from the nipple which may be haemorrhagic. Examination of the discharge will reveal benign epithelial cells.

Ductal carcinoma in-situ (DCIS)

The cells lining the ducts show cytological features of malignancy but have not yet invaded the stroma. Focal calcification allows it to be detected by mammographic screening or it may present as a palpable mass.



DCIS is graded into high and low grade, the former having a higher risk of invasive malignancy. Intraepithelial spread of DCIS into the nipple skin gives rise to Paget's disease.

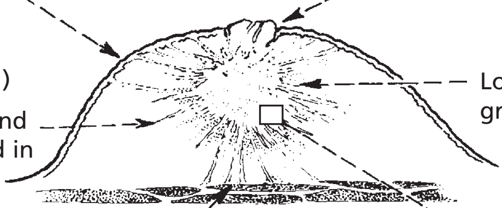
Lobular carcinoma in situ. This lesion is usually multifocal and bilateral. The breast acini of affected lobules are distended by fairly uniform cells which grow into the duct system or break through basement membrane to become infiltrative carcinoma, either of lobular or ductal type.

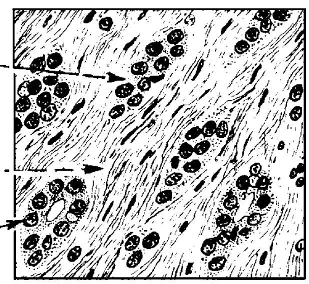
CARCINOMA OF THE BREAST

This is the commonest form of malignancy in women and rarely occurs in men. It may be found in any part of the breast but most frequently it is in the upper outer quadrant.

INFILTRATING DUCTAL CARCINOMA

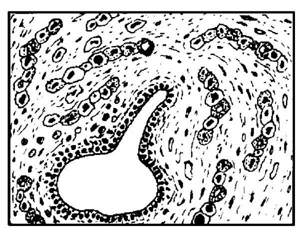
This, the commonest form, presents as a firm to hard lump. The following illustrations show a large carcinoma with significant local spread. It is emphasised that modern screening methods aim to detect the disease at a much earlier stage.



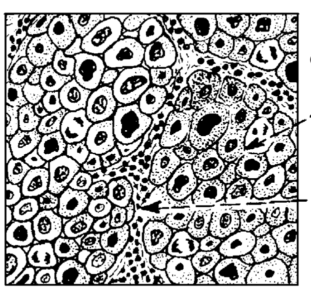


INFILTRATING LOBULAR CARCINOMA

Ten per cent of breast cancers are of this type. There is a 10% chance of a similar tumour arising in the contralateral breast. Microscopically the tumour infiltrates the tissues as single files of malignant cells.



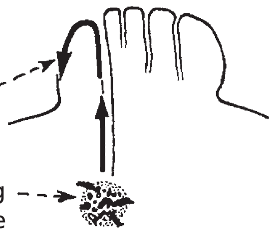
Infiltrating lobular carcinoma

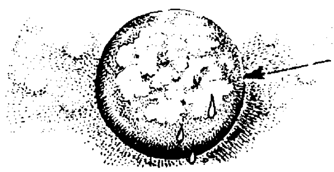


More rare forms of breast cancer are TUBULAR CARCINOMA – showing well differentiated cells often with intra-tubular calcification: MEDULLARY CARCINOMA – a highly cellular tumour with a florid lymphocytic infiltrate, and MUCINOUS CARCINOMA where the malignant cells lie in pools of mucin.

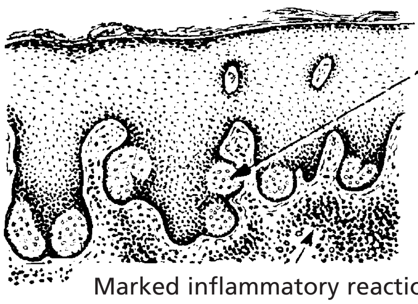
CARCINOMA OF THE BREAST

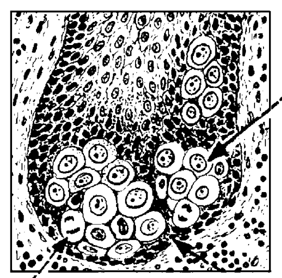
Local Spread: In late stages local infiltration causes skin ulceration and there may be direct penetration of the chest wall. Intra-epithelial spread occurs. The classical example is **PAGET'S DISEASE OF THE NIPPLE** – which may complicate intra-duct carcinoma.





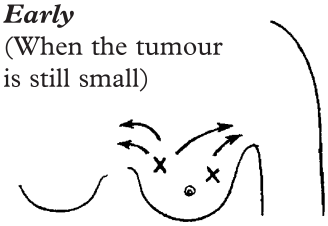
Microscopic examination reveals:





Metastatic Spread: This is by lymphatic and blood streams.

Early
(When the tumour is still small)



via LYMPHATICS
1. To axillary nodes from all sites of breast.
2. Through internal mammary lymphatics to thorax (esp. in cancers sited medially).

via BLOOD STREAM
to bone marrow where cells can lie dormant for long periods.

Late

Local spread via skin lymphatics causing:

(a) Widespread lesion – skin becomes stiff and board-like: 'cancer-en-cuirasse'.
(b) Blockage of dermal lymphatics: oedema of skin except at anchorage points, 'peau d'orange' (see p.241).

Secondaries appear in many viscera, particularly liver, lung and bone (spine, long bones)

CARCINOMA OF THE BREAST

Prognosis
The most important factors determining prognosis are:

1. Size – lesions under 1 cm rarely metastasise.
2. Number of lymph nodes involved – divided into three groups
   (a) no nodes involved
   (b) 1–3 nodes
   (c) ≥ 4 nodes.
3. Histological grade (graded 1,2,3) on the basis of
   (a) extent of tubule formation
   (b) nuclear pleomorphism
   (c) mitotic activity
4. Hormone receptor status – oestrogen receptor positive tumours respond better to tamoxifen and other anti-oestrogen drugs. Progesterone receptors are also detected. Demonstration of overexpression of the oncogene C-erb B-2 allows treatment by monoclonal antibodies (herceptin) directed against the protein.

These factors are summarised in prognostic indices such as the Nottingham Prognostic Index, based on size, lymph node status and grade.

Aetiology
Breast cancer is uncommon below the age of 30 years. The risk increases with age, the maximal incidence being in the later decades.
The important risk factors are:

1. **Genetic:**
There is a strong familial association. Mutation of genes, BRCA1 on chromosome 17 and BRCA2 on chromosome 11, are responsible for many cases of breast cancer in young women with a positive family history. Deletion of tumour suppressor genes has been identified (mutation of suppressor gene p53 is common) – Li–Fraumeni syndrome.

2. Sex hormone associations:
   (a) Commoner in nulliparous women.
   (b) Early menarche and late menopause increase risk – ? prolonged cyclical exposure to sex hormones.
   (c) Breast feeding reduces risk.

Screening for Breast cancer
The aim of screening is to detect either pre-malignant conditions or cancer at an early stage and is very important where there is a family history of cancer. Mammography is capable of detecting intra-duct carcinoma and pre-cancerous lesions. Focal calcification is an important indicator but is not diagnostic of malignancy because it also occurs in benign lesions. Whatever method of screening is used the diagnosis must be established on morphological evidence using fine needle aspiration, needle biopsy and, sometimes, open biopsy.

Other rare tumours of the breast include PHYLLODES TUMOUR – large and usually benign, affecting elderly women: occasionally sarcoma of the stroma is present. Soft tissue sarcomas and primary lymphoma are rare.

THE MALE BREAST
Breast disease is uncommon in men. Abnormal enlargement – gynaecomastia – may occur in a temporary form at puberty or as a permanent feature in Klinefelter's syndrome (XXY). Oestrogen metabolic upsets (e.g. in liver disease) or excess intake (e.g. treatment of prostatic cancer) are other causes. All tumours are rare but breast cancer does occur.

CHAPTER 14

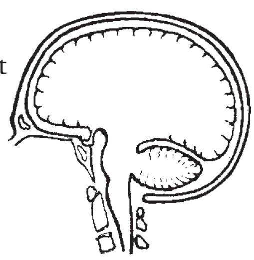
NERVOUS SYSTEM

NERVOUS SYSTEM – ANATOMY AND PHYSIOLOGY

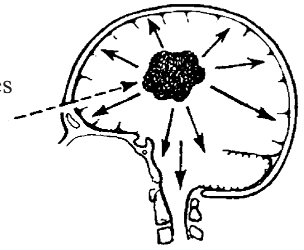
Considerations of anatomy and physiology have important applications to diseases of the central nervous system (CNS), particularly their effects and spread.

The anatomy of the various coverings is important.

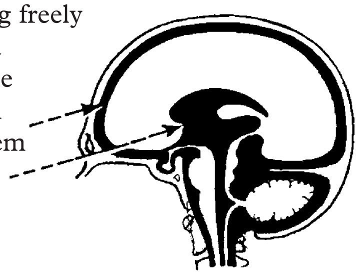
The skull and vertebrae form a rigid compartment protecting the delicate CNS tissues.



This rigidity has serious disadvantages when pressure inside the skull increases, e.g. an expanding lesion soon takes up the small reserves of space available and the delicate brain tissues are progressively compressed, with very serious results.

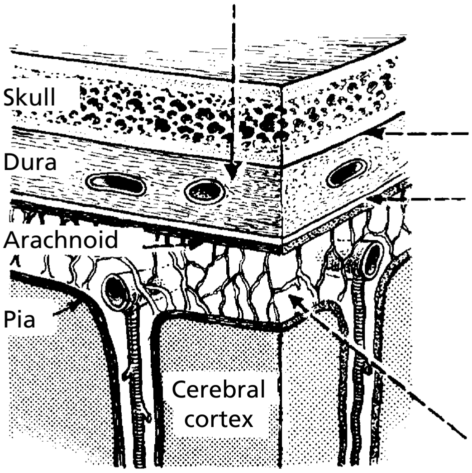


Meninges and cerebrospinal fluid (CSF)
The CSF circulating freely in the subarachnoid space over the whole CNS surface and in the ventricular system acts as a protective water bath.



Diseases (particularly infections) at this site are usually *widespread* over the whole brain and cord surfaces, e.g. meningitis. Impediment to the flow of CSF causes serious effects – hydrocephalus.

The detailed arrangement of the meninges is important.
The thick **dura**, closely applied to the skull, acts as the periosteum – its rigid reflections (falx cerebri and tentorium cerebelli) complicate the effects of increased intracranial pressure.



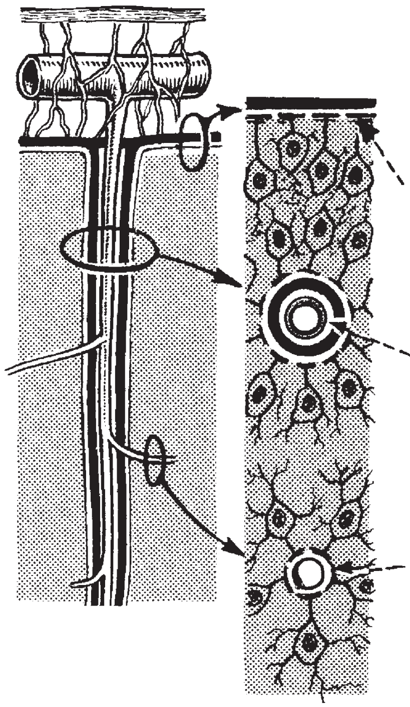
Extradural lesions tend to be localised; they have to strip the dura from the bone.
Subdural lesions remain local but can spread more widely since the arachnoid and dura are loosely attached.
The **arachnoid**, a delicate membrane, is loosely attached to the dura and sends trabeculae across the subarachnoid space which contains the cerebral blood vessels and the CSF.
Disease in the **subarachnoid** space can spread widely over the whole surface of the brain and spinal cord but is prevented from penetrating into the brain tissue by the **pia**.

NERVOUS SYSTEM – ANATOMY AND PHYSIOLOGY

The **pia** is invaginated into the brain substance along with the small penetrating vessels.

The dura, arachnoid and pia act as barriers which selectively separate the CSF and the blood from the CNS tissues.

It is important to understand that, although the CSF is very similar in composition to the extracellular fluid of the brain, changes in the CSF only very indirectly reflect changes in the CNS in disease.



The pia's barrier function is reinforced by the membrane formed by the foot processes of astrocytes:

1. on the brain surface
2. around the penetrating vessels. The potential space between the vessel wall and the pia is called the Virchow–Robin space.
3. at capillary level the pia is not present, but the foot processes along with the capillary endothelium and basement membrane form a specialised and selective 'blood-brain barrier'.

Thus the pia and the membrane formed by the foot processes of the astrocytes separate types of tissue derived from two embryological layers.

(1) **Neuroectodermal**
i.e. CNS tissue
consisting of
Neurones
Neuroglia → Ependyma, Astrocytes, Oligodendroglia

Pia

(2) **Mesodermal**
i.e. Blood vessels,
meninges (fibrous tissues)

and

MACROPHAGES → MICROGLIA (most are resident round blood vessels)

During embryological development these enter the CNS tissues proper and become microglia

These SPECIALISED tissues are subject to INJURY and DEGENERATIVE processes.

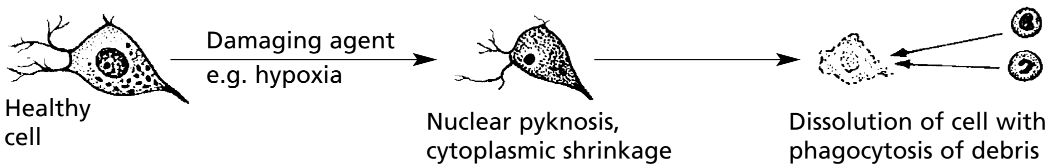
These tissues behave similarly to mesodermal tissues elsewhere in the body, e.g. INFLAMMATORY RESPONSE.

NEURONAL DAMAGE

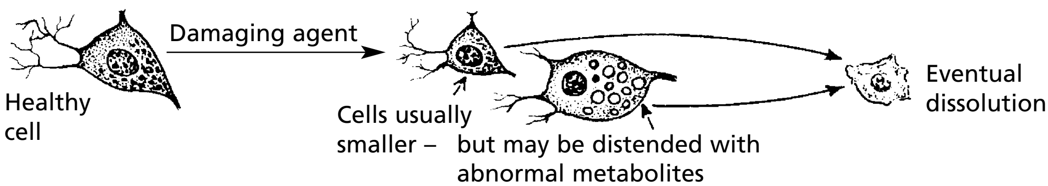
NEURONES are sensitive to damage by a wide variety of agents including anoxia, hypoglycaemia, virus infections and intracellular metabolic disturbances (e.g. associated with vitamin B deficiencies).

There are two main types, depending on the rapidity of the changes.

1. *Rapid NECROSIS* – associated with acute failure of function.

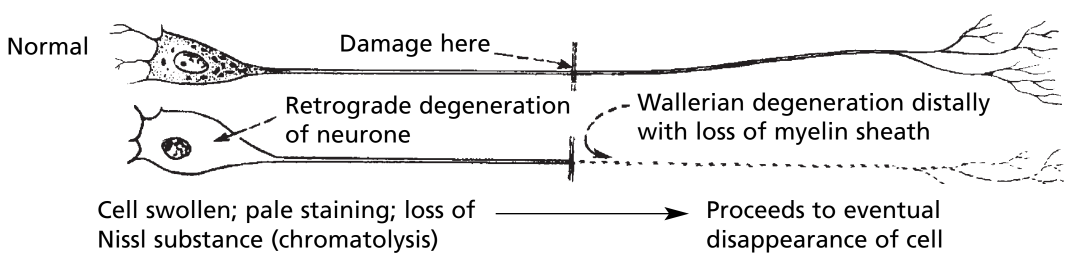


2. *Slow ATROPHIC CHANGES* – associated with gradual loss of function.

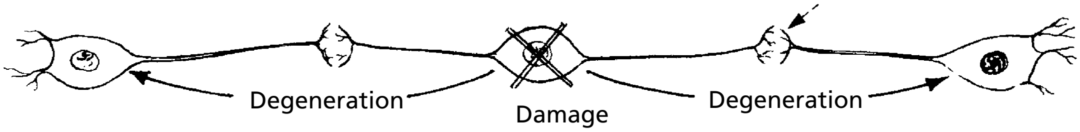


The process of ageing involves cumulative atrophy and disappearance of neurones; in some individuals the process is speeded up resulting in ***presenile dementia***.
Note: There is no regeneration of destroyed neurones.
A large group of disorders of cerebral function seen in psychiatric practice have (as yet) no morphological evidence of nerve cell damage. They are caused by disturbances of poorly understood biochemical control mechanisms within the brain.
In addition to the PRIMARY degenerations described above, neurones are subject to SECONDARY degeneration in certain circumstances.

1. ***Retrograde degeneration*** – when the main axon is damaged there is degeneration of the neurone as well as the classical distal degeneration of the axon.



2. ***Trans-synaptic degeneration*** – in closely integrated neurone systems, neurone loss may be followed by degeneration of associated neurones across synapses.

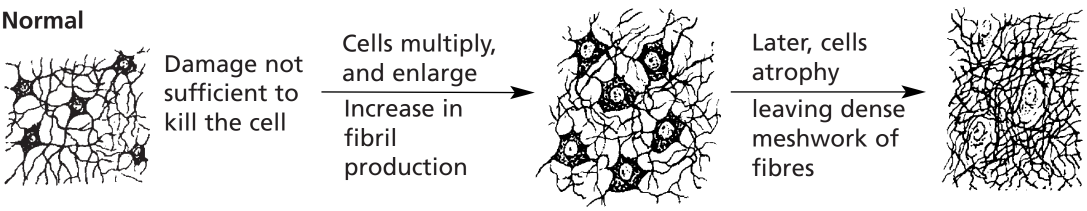


GLIAL REACTIONS

The glial cells react vigorously in many diseases of the CNS.

1. The **NEUROGLIAL** cells have supportive and nutritive functions.

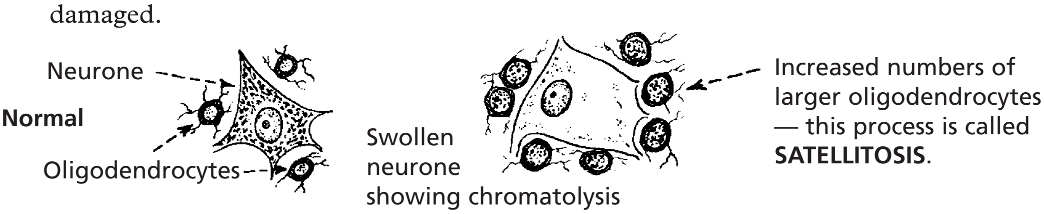
(a) The **astrocytes** with their numerous fibrillary processes give structural support. They are less susceptible to damage than neurones.



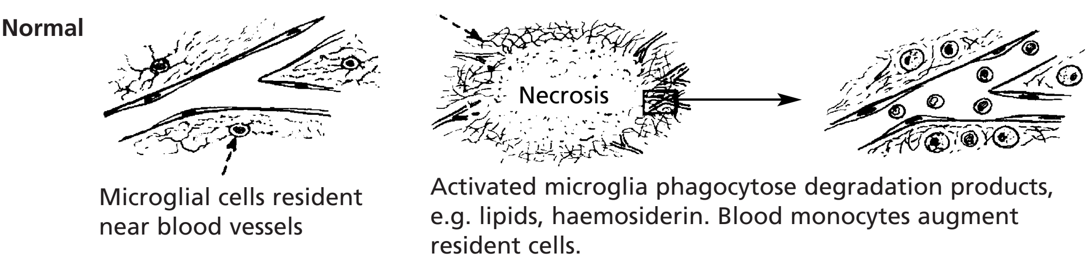
This process is called GLIOSIS. It is a feature of many diseases and is analogous to scar tissue. These cells and fibres contain Glial Fibrillary Acidic Protein (GFAP), recognition of which, using antibodies, is useful in histological sections.

Note: Collagenous scar tissue is only formed in the CNS when mesodermal structures such as large blood vessels are damaged.

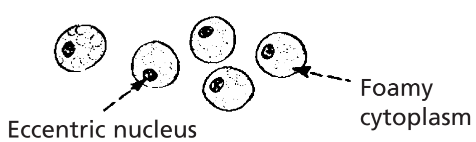
(b) The **oligodendrocytes** – small cells with short processes – have a nutritive function in respect of neurones and especially myelin. This reaction is best seen when neurones are damaged.



2. The **MICROGLIAL** cells are members of the mononuclear-phagocytic system. Reaction is best seen when there is necrosis of tissues.



Microglial cells are well seen in and around infarcts; the activated cells which have ingested lipids are strikingly different from the small inactive microglia.



These cells have been given a variety of names: e.g. 'gitter' cells, or lipophages (lipid phagocytes).

INCREASED INTRACRANIAL PRESSURE

INCREASED INTRACRANIAL PRESSURE (ICP) occurs in two main circumstances:

1. Due to the presence of an EXPANDING LESION
2. Due to obstruction of the free flow of the CSF – this causes hydrocephalus and is dealt with on page 570.

INTRACRANIAL EXPANDING LESIONS

These lesions may occur within the brain substance or in the meninges. Important examples are:

INTRACEREBRAL

Haemorrhages and haematomas → Traumatic or spontaneous

Infarction

Tumours → Primary cerebral or secondary

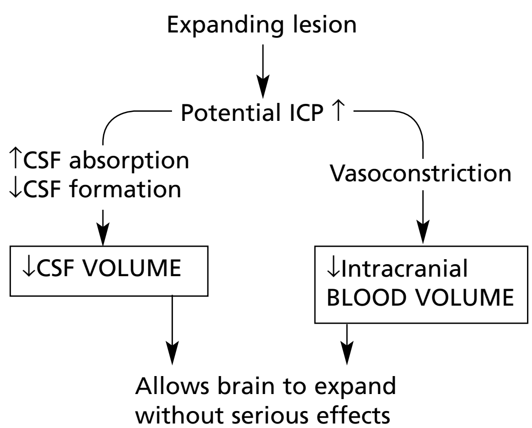
MENINGEAL

Haemorrhages and haematomas → Usually traumatic
- (a) Extradural
- (b) Subdural
- (c) Subarachnoid

Very occasionally meningioma.

The situation is often aggravated by cerebral OEDEMA.
The severity of the effects is modified by two important factors:
(1) the size of the lesion and (2) the rapidity of expansion.
There are three stages in the progress of increased intracranial pressure (ICP).

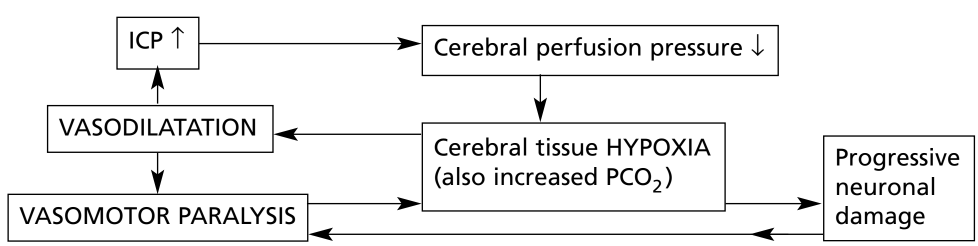
(1) The stage of **Compensation**



(2) The stage of **Decompensation**

At this stage there are herniations and distortions of the brain with their associated complications including:
- reduction in level of consciousness
- dilatation of pupil ipsilateral to mass lesion and papilloedema
- bradycardia with raised blood pressure ('Cushing' effect)
- Cheyne–Stokes' respiration

(3) A vicious circle is established leading to the stage of **vasomotor paralysis**.

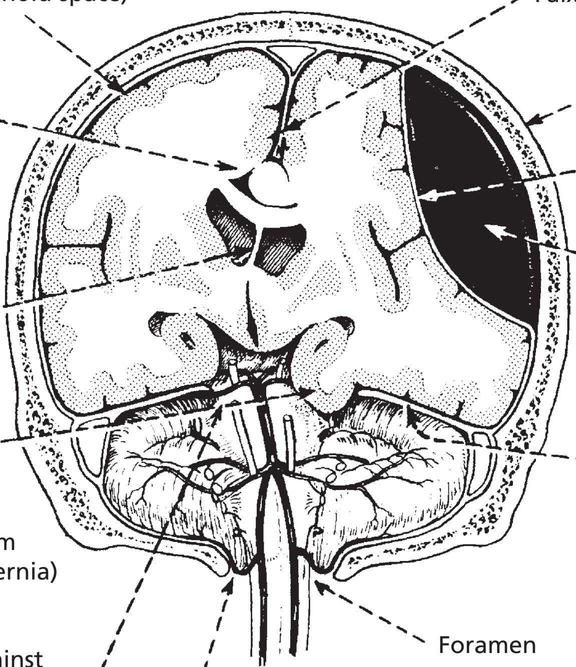


INCREASED INTRACRANIAL PRESSURE

Effects

DISTORTIONS and DISLOCATIONS of the brain substance

These are to some extent dependent on the site of the initiating lesion; the effects of a unilateral expanding lesion are illustrated.



Note: The sudden removal of even small amounts of CSF by LUMBAR PUNCTURE may precipitate medullary ‘coning’ with fatal results due to damage to the ‘vital centres’.

CEREBRAL OEDEMA

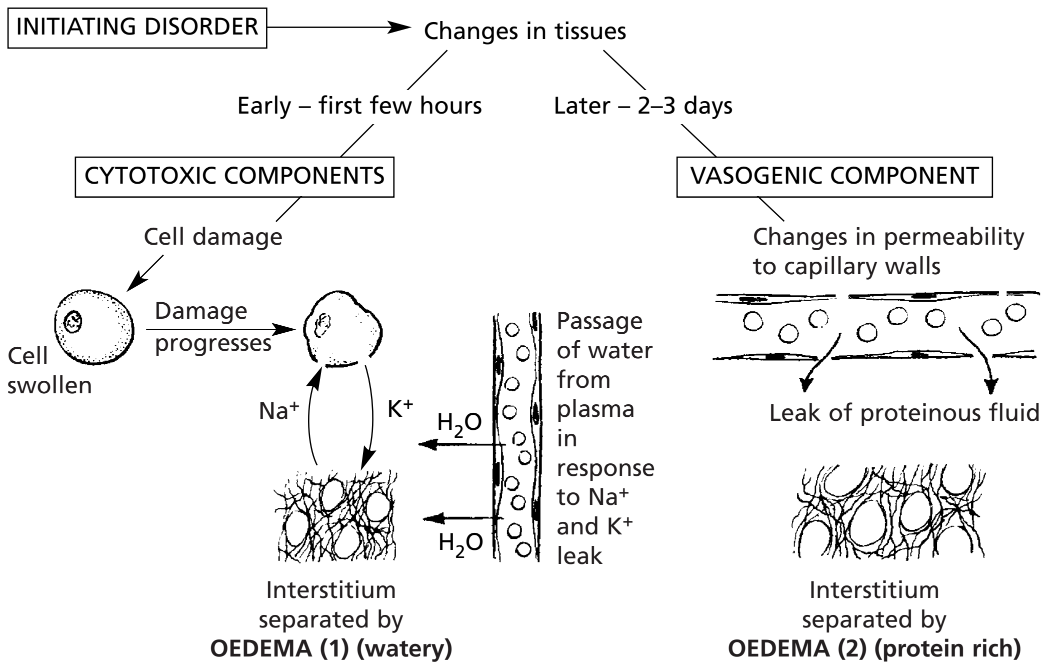
Swelling of the brain, of which oedema is the major component, is an important complication of many brain diseases because the enlargement either initiates or aggravates increased intracranial pressure.

The process may be localised or generalised depending on the type of initiating disorder.

Localised conditions
Examples:
- Infarcts, and local ischaemia
- Haematomas (due to vessel rupture and injury)
- Tumours

Generalised conditions
Examples: Intoxications
- Metabolic disturbances, e.g. hypoglycaemia
- Generalised hypoxia
- Severe head trauma
- Malignant hypertension

The pathological mechanism is as follows:



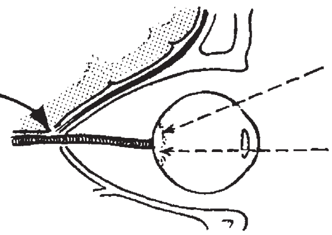
Notes
(a) Components (1) and (2) overlap.
(b) The oedema fluid tends to spread in the white matter.
(c) The severity of oedema formation is very variable and unpredictable clinically.
(d) In clinical practice, therapy has two aspects:
  1. Treatment of the initiating disorder by any appropriate means.
  2. Minimising the formation of oedema by the use of
     (i) osmotic agents, e.g. urea or mannitol
     (ii) steroids.

INCREASED INTRACRANIAL PRESSURE

SECONDARY COMPLICATIONS

1. **Vascular damage**

(a) Compression of the central retinal vein causes PAPILLOEDEMA, an important clinical sign of raised ICP. *Note:* Axonal flow in the optic nerve is reduced, contributing to swelling of the optic disc.

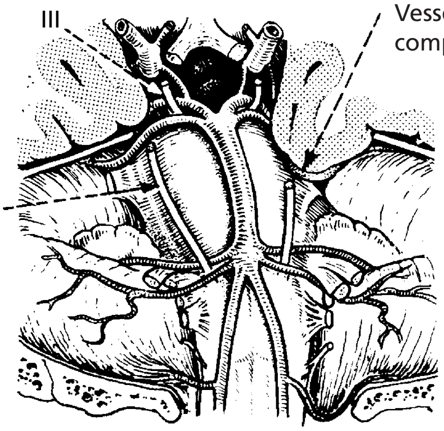


(b) Stretching and compression of blood vessels may cause haemorrhage and infarction quite remote from the initiating lesion – secondary midbrain and calcarine infarction and haemorrhage are common.

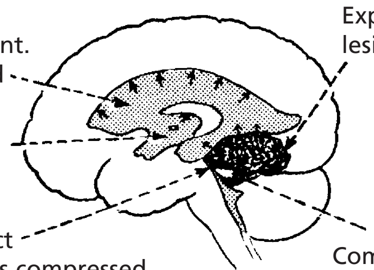
2. **Intracranial nerve damage**

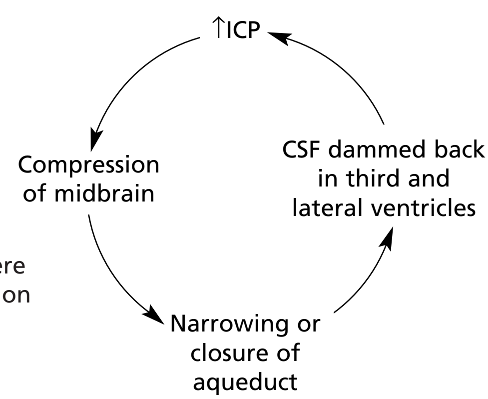
Oculomotor (III) and abducens (VI) nerves are particularly prone to damage, giving rise to paralysis of ocular movements in varying combinations.

The VIth nerve is specially vulnerable due to its long subarachnoid course. It is often the nerve on the side opposite the lesion which is stretched giving rise to paradoxical signs.



3. **Obstruction of flow of CSF**





4. **Changes in the skull bones**

Long continued ICP causes bone erosion and thinning visible on X-ray.

(a) Erosion of posterior clinoid processes of sphenoid bone.

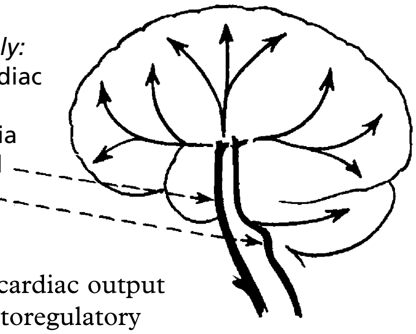
(b) In children, before the skull is fully ossified, the inner table is thinned at the sites of convolutional pressure giving a striking X-ray appearance.

CIRCULATORY DISTURBANCES

(1) Hypoxia and ischaemia and (2) intracranial haemorrhage are the important and common mechanisms causing brain damage.

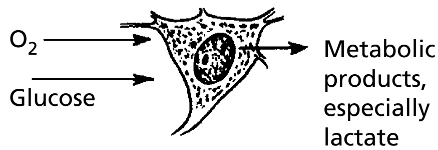
ACUTE HYPOXIC DISORDERS

Blood supply: 20% of cardiac output is delivered via carotid and vertebral arteries



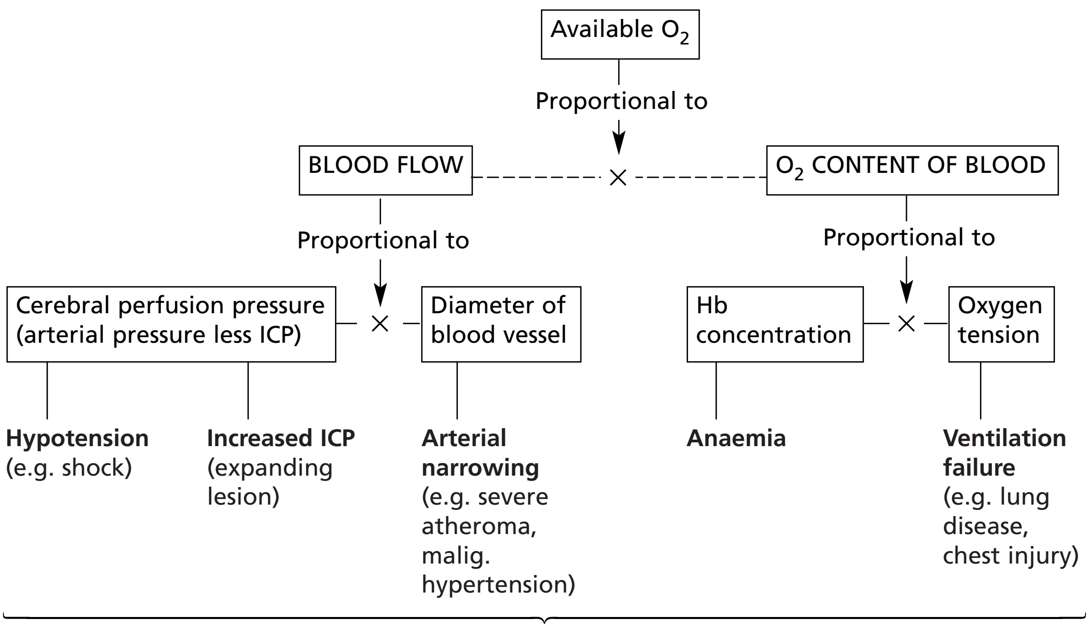
When the cardiac output falls, an autoregulatory vascular control mechanism protects the cerebral blood supply – the arterial BP must be kept above 50 mmHg.

Neuronal aerobic metabolism of glucose



There are no reserves of O_2 or glucose in the brain, therefore a constant delivery via arterial blood is necessary.
Neurones are very susceptible to hypoxia (and hypoglycaemia); with complete O_2 deprivation neuronal **necrosis** occurs in 5–7 minutes (at normal temperatures).

The following flow diagram illustrates the factors which influence availability of O_2 and the conditions giving rise to hypoxia.



These conditions, singly or together, can be responsible for cerebral hypoxia.

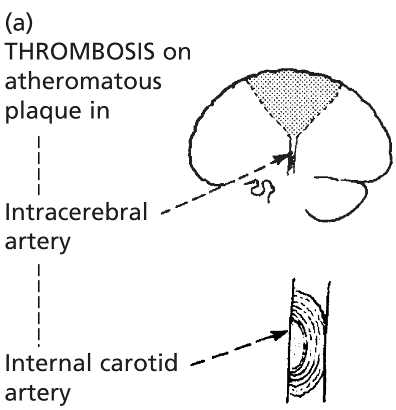
CEREBRAL INFARCTION

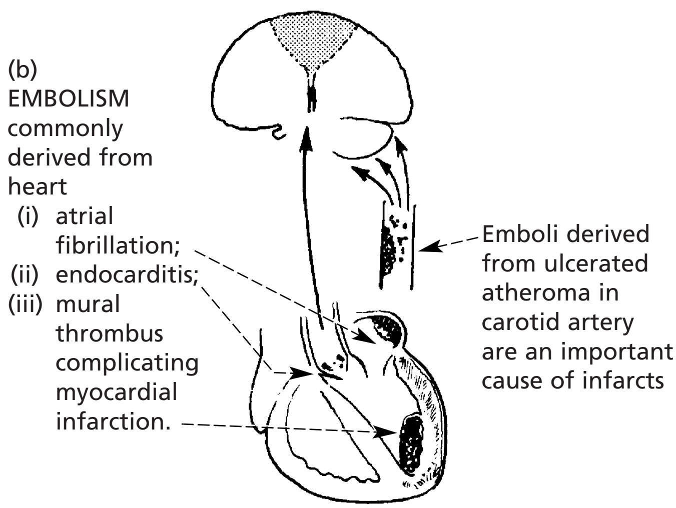
This condition, the commoner of the two main types of stroke (the other is spontaneous intracerebral haemorrhage), is caused by failure of the supply of oxygen (and glucose) to maintain the viability of the tissues in the territory of a cerebral arterial branch. This is not always due to simple local arterial occlusion, and very often a component of central circulatory deficiency is contributory. The lesion is essentially necrosis of all the tissues in the affected territory.

Mechanism
Precipitating condition ⟶ Perfusion failure ⟶ INFARCTION (ischaemic necrosis)

LOCAL ARTERIAL DISEASE (particularly ATHEROMA) and its complications, are the most common.

1. **Arterial occlusions**





2. **Arterial stenosis**

ATHEROMA – the widespread loss of arterial lumen potentiates cerebral perfusion deficiency in two ways: (1) by distributing the normal arterial flow and (2) by prejudicing anastomotic communications.

Atheromatous stenosis alone is not usually a cause of infarction, but when central circulatory deficiency is added, infarction is common, e.g. this may vary from the slight fall in BP during sleep to the severe hypotension of shock or myocardial infarction.

Other rarer causes of arterial stenosis are dissecting aneurysm and arteritis. Arterial spasm is even rarer.

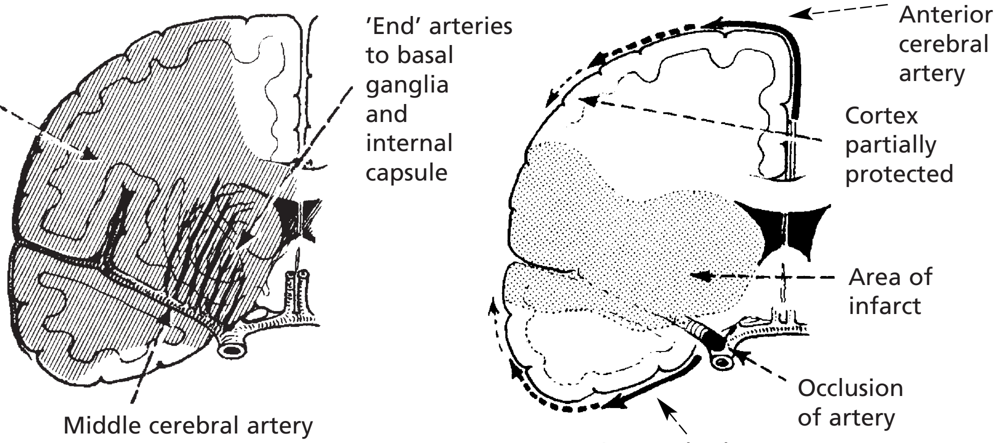
Cerebral infarction can now be treated by administering ‘clot busting’ drugs. To avoid permanent damage these need to be given within 3 hours of the onset of symptoms. Tissue plasminogen activator which converts plasminogen to plasmin is most frequently used. Cerebral bleeding is a potential side effect. Alternatively thrombus can be surgically removed from the carotid artery. The success of these treatments is variable.

CEREBRAL INFARCTION

SITES

While infarcts may occur anywhere in the brain, depending on the vagaries of the precipitating arterial lesions, certain sites are more commonly affected.

1. In cases of local arterial occlusion, **internal structures supplied by 'end' arterial branches** are particularly vulnerable. The cortex is often protected in variable degree by anastomoses of other cerebral arteries. This is illustrated in the territory of the middle cerebral artery.



2. **Boundary zones** (see p.177)

   The cortex in particular is damaged in boundary zone infarction. In these cases, central circulatory deficiency is an important component, e.g. hypotension.

BRAIN DAMAGE DUE TO CARDIAC ARREST

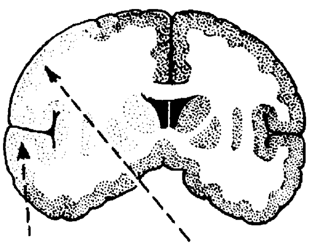
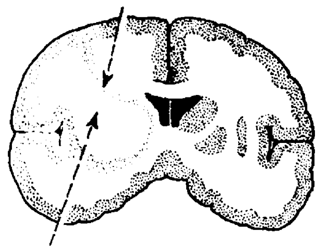
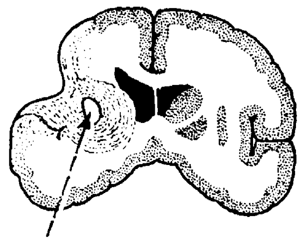
This is characterised by widely distributed selective neuronal necrosis – the neurones are more susceptible to hypoxia than the supporting cells.

Affected areas – total cortical necrosis
or
most sensitive zones – hippocampus
– layers III, V, VI of cortex
– within sulci
– Purkinje cells of cerebellum.

Note: (a) These changes do not become apparent unless the patient survives at least 12 hours after the arrest.
(b) Similar types of neuronal damage can be seen in severe acute hypoglycaemia, carbon monoxide or barbiturate poisoning.

CEREBRAL INFARCTION

The diagram below illustrates the evolution of an infarct, e.g. in the territory of the middle cerebral artery. Up to 24 hours there is virtually no visible change.

18–24 hr	After 24 hours	After a few days	After weeks/months
Gross appearances			
Very difficult to see	Less difficult to see  Slight swelling; Blurring of white/grey junction	Line of demarcation seen  Necrotic tissue. Soft to touch; usually pale but may be congested if blood has permeated in (haemorrhagic infarct)	Demolition + scarring  Cyst with pale or yellowish fluid; Shrinkage of scarred area: compensatory dilatation of ventricle
Microscopic appearances			
Early neuronal damage	Early neuronal damage → Necrosis of neurones	Organisation of infarct begins Macrophages appear; capillary sprouting; oedema diminishing	Organisation well established; neurones disappear; numerous macrophages; gliosis
Clinical associations			

FUNCTIONAL LOSS

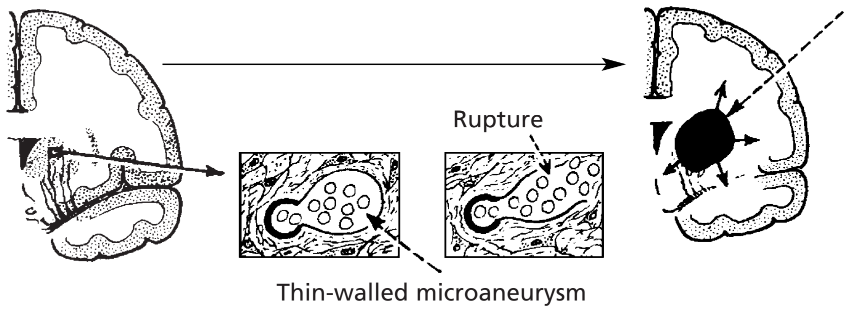
Effects are maximal in the early stages when oedema and circulatory disturbance in the adjacent tissues augment the functional loss caused by infarct. Larger infarcts may be associated with loss of consciousness.

The prognostic assessment of final functional loss cannot be made until the changes have subsided and any possible functional compensations have been established. This takes many weeks. Complete clinical recovery may follow small infarcts. Prompt thrombolytic therapy with tissue plasminogen activator can limit the degree of permanent disability.

CEREBRAL HAEMORRHAGE

Spontaneous intracranial bleeding is the second main type of stroke. In the great majority of cases there is localised arterial disease aggravated by hypertension. A small number are associated with cerebral tumours, systemic bleeding diathesis or arteriovenous malformations.

In most hypertensives over middle age, **microaneurysms** are found in the very small cerebral arteries. It is believed that rupture of one of these aneurysms is the immediate cause of intracerebral haemorrhage.



Progress
The onset is usually sudden with headache and, because of the high blood pressure, progress is rapid and the haemorrhage large.

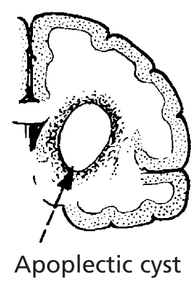
↓

Associated raised ICP effects

↓

Death in many cases

When the bleeding is limited, there is survival with varying residual paralysis.



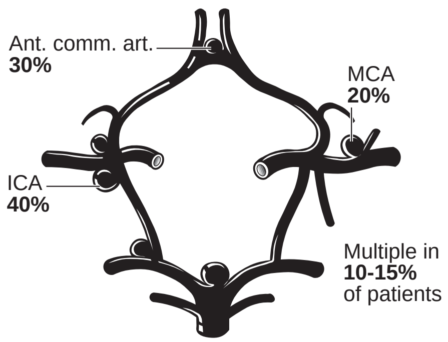
Final outcome
Cystic space containing yellow-brown fluid walled off by gliosis.

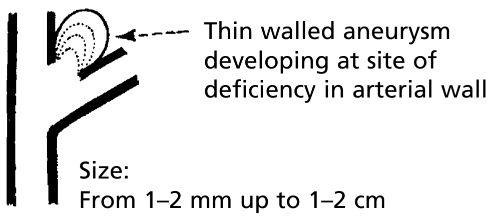
Note: Intracerebral bleeding may track irregularly and often reaches the subarachnoid space and ventricles.

SUBARACHNOID HAEMORRHAGE

This is commonly but not exclusively the result of rupture of a 'berry' aneurysm at or near the circle of Willis. The basic abnormality is a congenital weakness of the elastic tissues in the arterial wall; only rarely is an aneurysm present at birth, and while subarachnoid haemorrhage does occur in young people, the incidence increases with age. Hypertension is an important contributing factor.

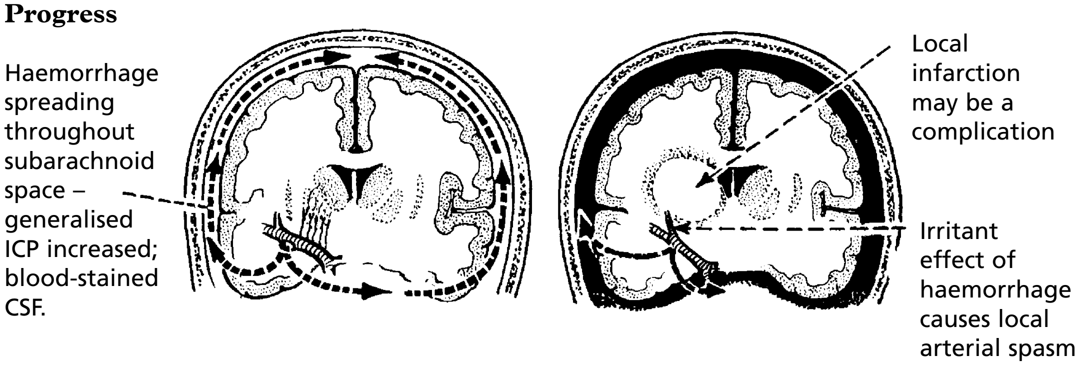
Sites Often multiple, near arterial junctions.





Not all aneurysms rupture; they are found incidentally at autopsy.
Massive haemorrhage may be preceded by one or more small leaks – marked by headache without functional loss.

Progress



Note: The aneurysm may rupture directly into the brain and mimic an intracerebral haemorrhage.

CSF findings

1–24 hours – blood stained; blood content constant in sequential samples (distinguishes blood derived from a traumatic tap)
– centrifuge supernatant – may be pink due to haemolysis.

24 hours onwards – supernatant shows xanthochromia (yellow colour due to presence of blood degradation products).

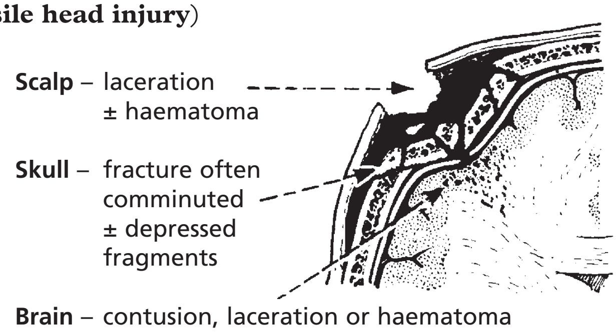
Other causes of cerebral haemorrhage of either type are vascular malformations and coagulation disorders.

HEAD INJURY

Head injuries of varying severity are common nowadays, particularly as a consequence of road traffic accidents. Immediate damage is caused by two main mechanisms which overcome the protection of the vulnerable cerebral tissues provided by the skull and the CSF 'water cushion'.

1. **Direct blows to the head** (e.g. **missile head injury**)

usually cause injury to the soft tissues of the scalp and often fracture of the skull with contusion or laceration of the underlying brain.

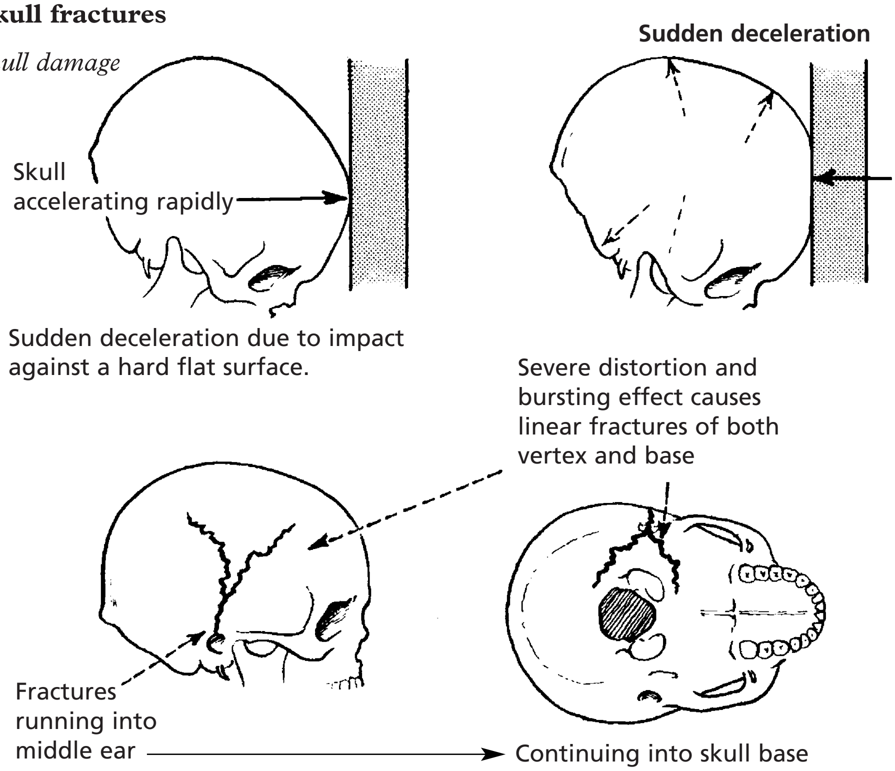


2. **Non-missile head injury**

Since the head is usually freely moveable on the neck, the sudden application of forces derived from **acceleration, deceleration** and, particularly, **rotation** of the head often causes serious brain injury.

(a) **Skull fractures**

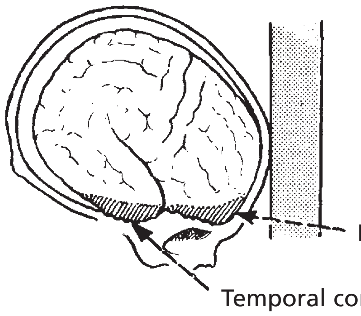
(i) *Skull damage*

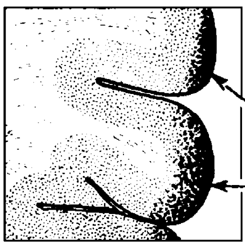


HEAD INJURY

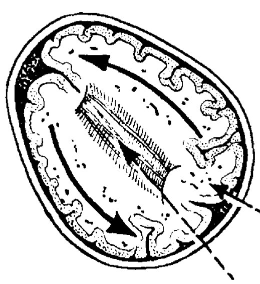
Acceleration/deceleration injury

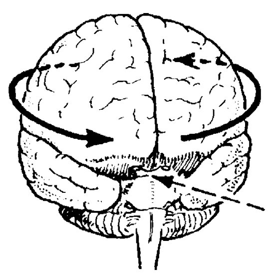
(ii) *Brain damage*

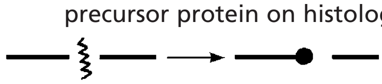




(b) **Rotation**







Note:
It will be appreciated that more serious cerebral damage is the result of interaction of complex physical forces and anatomical features. An understanding of these mechanisms explains why serious cerebral injury is not uncommon in the absence of damage to the scalp or fracture of the skull, and also why brain damage may be remote from the site of impact: so-called ‘contre-coup’ injury is sustained when the brain tissue opposite the site of impact is contused.

HEAD INJURY

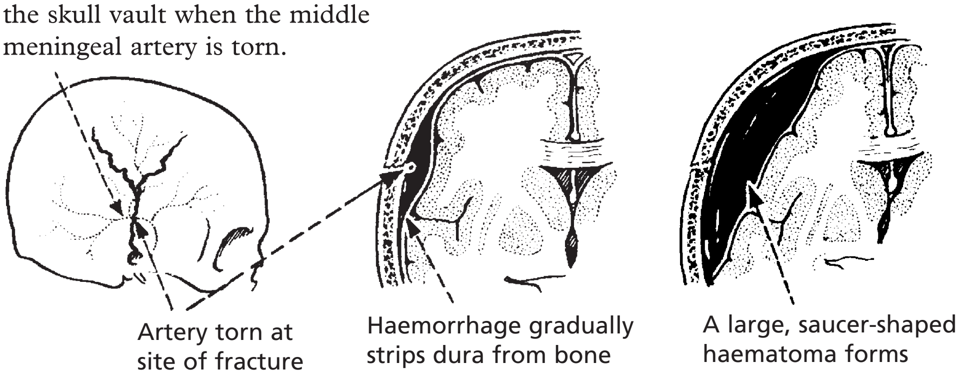
DELAYED COMPLICATIONS

In addition to damage sustained immediately at the time of impact, certain serious complications may supervene over the next hours or few days.

1. **Haemorrhages**

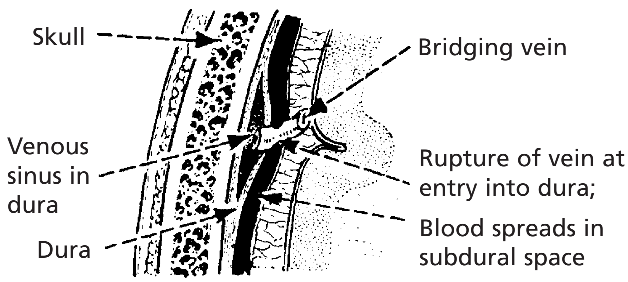
(a) **Extradural haematoma**

This type of haemorrhage classically occurs as a complication of linear fracture of the skull vault when the middle meningeal artery is torn.



The classic clinical association is a direct blow to the head from which recovery is rapid. After a lucid interval of varying duration up to several hours, signs of increased intracranial pressure supervene. This chain of events is explained by the time taken for the haemorrhage to accumulate by stripping the dura from the skull.

(b) **Subdural haematoma**. This may occur at any site and is often extensive because of the loose attachment of the dura and arachnoid membranes. It is usually due to rupture of small bridging veins.



These acute subdural haematomas are often associated with subarachnoid haemorrhage and cerebral contusions.

(c) **Intracerebral haematomas** occur in association with cortical contusions particularly in the temporal and frontal lobes (burst lobe); but also at random deep within the hemispheres due to shearing at the time of impact. Large haematomas are uncommon.

HEAD INJURY

Delayed complications (*continued*)

2. **Cerebral oedema** is an important complication.

   ↓

   Increased intracranial pressure ⟶ Cerebral hypoxia.

3. **External leakage of CSF** (and blood) from the ear and nose may complicate fractures of the skull base. This complication may be of long duration and is always a potential entry for infection.

4. **Local infection** may complicate compound fractures and progress to meningitis.

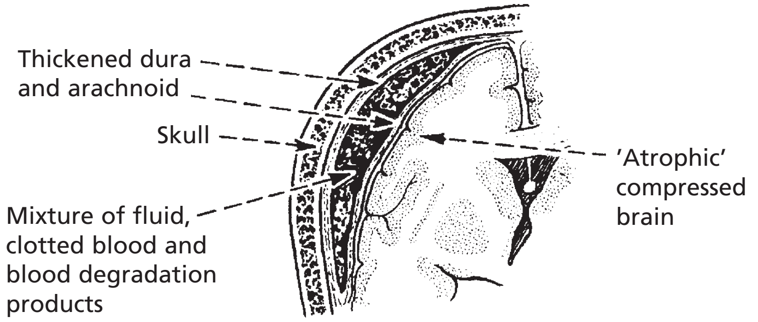
LATE COMPLICATIONS

1. **Epilepsy**

   Head injury is an important cause of epilepsy. The risk is highest in severe missile head injury and may be related to ischaemic brain damage.

2. **Chronic subdural haematoma**

   A thick layer of fluid and partially clotted blood gradually accumulates between the dura and arachnoid membranes which show considerable reactive thickening.



The precise cause is not known; most cases occur in alcoholics or in elderly people already suffering from cerebral atrophy, and it is possible that the small bridging veins are unduly stretched and become more susceptible to damage.

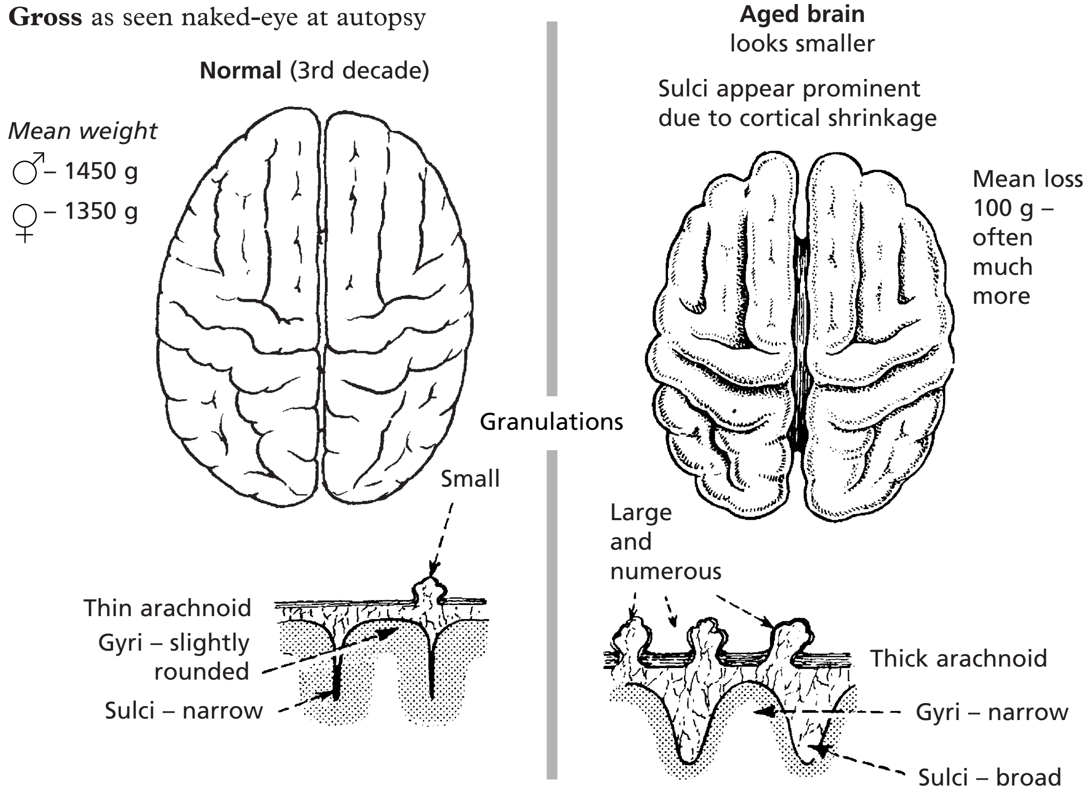
The clinical signs are usually insidious in onset and progressive, and in many cases there is a history of either no or only very trivial injury.

AGEING and DEMENTIA

Normal Brain Ageing
With normal ageing the brain becomes atrophic, but the morphological changes described below are not necessarily accompanied by loss of intellect.

Changes in old age

Gross as seen naked-eye at autopsy



There is compensatory enlargement of the lateral ventricles.

Dementia
Dementia is defined as 'an acquired progressive global impairment of intellect, memory and personality, without impairment of consciousness'. Around 5% of the population over 65 years are affected and the proportion rises to over 20% of these over 80 years.

Main causes are:
1. Alzheimer's diseases 70%
2. Multi-infarct dementia 10–15%
3. Lewy body dementia 10–20%

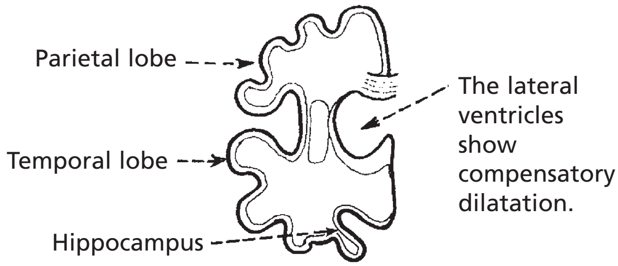
Rare causes include:

1. Genetic disorders (Huntington's disease, Pick's disease)
2. Infections (Creutzfeld–Jacob disease, see p.555, AIDS)

ALZHEIMER'S DISEASE

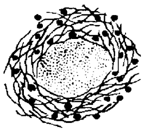
This disease accounts for around 70% of cases of dementia. While typically a disease of the elderly, especially females, it is also seen in patients under 60 years, in whom there is often a family history. Almost all patients with Down's syndrome who survive to 50 years develop Alzheimer's (suggesting that chromosome 21 is important).

Pathology
The changes of Alzheimer's resemble those of normal ageing, but are greatly exaggerated in the temporal and parietal lobes and in the hippocampus.



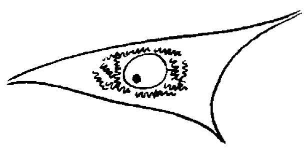
The histological hallmarks are:

1. Extracellular senile plaques.



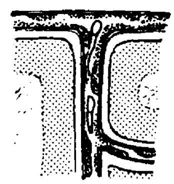
Tangled aggregates of distended neurites presenting as black dots and rods with a centre core of amyloid β-protein.

2. Intracellular neurofibrillary tangles.



Paired helical filaments composed of tau protein form around the nuclei of neurones.

3. Amyloid angiopathy.



Deposited in meninges and blood vessel walls.

4. Loss of neurones and synapses.

Pathogenesis – this is not fully understood but the theories include:

1. *Amyloid Hypothesis* – this theory postulates that amyloid β products are the cause of the disease. Accumulation of amyloid triggers neuronal degeneration, disrupts calcium homeostasis, induces apoptosis and builds up in mitochondria where it inhibits enzyme function. The amyloid hypothesis is supported by genetic factors (see below).
2. *Inflammatory Hypothesis* – this theory postulates that when normal brain tissue is disrupted as a result of inflammation, this can cause misfolding and, subsequently, accumulation of amyloid β. The effects may accumulate over many years as an acceleration of normal cellular senescence. Individuals who take anti-inflammatory drugs have a lower risk of Alzheimer's disease.

Genetic factors – several genes are involved

1. Amyloid precursor protein (chromosome 21) – early onset Alzheimer's.
2. Presenilin 1 and 2 (chromosome 14 and 1) – proteins involved in binding amyloid precursor proteins.
3. Apolipoprotein E – the E4 allele is associated with late onset disease.
   – it may determine the age of onset.
   – 40–80% of the those with Alzheimer's disease have at least one Apo E4 allele.
4. α-2 macroglobulin – may be involved in clearance of amyloid proteins.

DEMENTIA

MULTI-INFARCT DEMENTIA

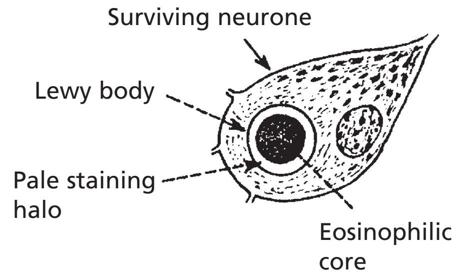
This form of dementia is associated with vascular disease – with infarcts often in the middle cerebral arterial distribution. The volume of brain loss appears to be important.

Loss of >100 ml of brain correlates with dementia.

Hypertension is an important underlying factor. A stepwise progression is typical.

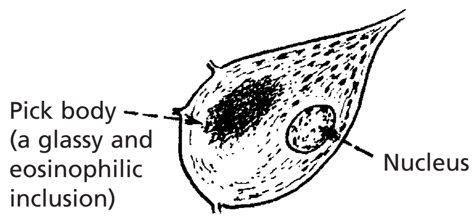
LEWY BODY DEMENTIA

This disorder accounts for 10–20% of dementias. Clinically there are overlapping features with Parkinson's disease. There is widespread neuronal loss in the cerebral cortex. Characteristic Lewy bodies are identified in surviving neurones. Known components of Lewy bodies include alpha-synuclein and ubiquitin.



PICK'S DISEASE

This uncommon form of dementia has a strong familial (autosomal dominant) component. There is typically severe atrophy of the temporal and frontal lobes. The histological marker in the surviving neurones is the Pick body.

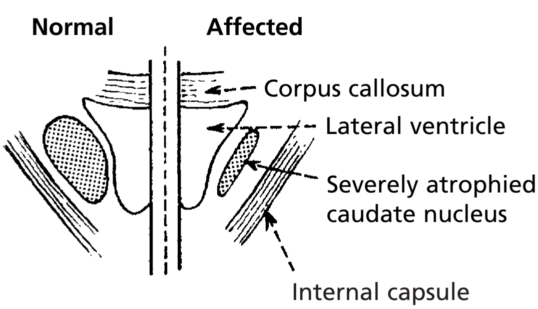


HUNTINGTON'S DISEASE

This is an uncommon autosomal dominant condition beginning in the 3rd or 4th decade and characterised by psychiatric disorders, progressive dementia and in some patients bizarre writhing movements (chorea).

Pathology

The caudate nucleus is severely atrophic. The genetic locus is on chromosome 4 and consists of a trinucleotide repeat with up to 34 copies in unaffected patients. In Huntington's disease the number of repeats increases with each successive generation resulting in earlier onset of symptoms (genetic anticipation). Genetic screening is available.



PUNCH DRUNK SYNDROME (DEMENTIA PUGILISTICA)

Professional boxers may develop dementia due to neuronal damage caused by repeated blows to the head.

INFECTIONS

Compared with the high incidence of infection generally, infection of the central nervous system is uncommon. The pathological effects may be slight and wholly recoverable as in some virus infections, or severe, leading to permanent damage or death.

Anatomically, infections fall into two main groups which tend to remain separated due to the intervention of the **pial** barrier (see p.527).

Infection ⟶ inflammation of ⟶ MENINGES (meningitis)

Infection ⟶ inflammation of ⟶ BRAIN SUBSTANCE (encephalitis; abscess)



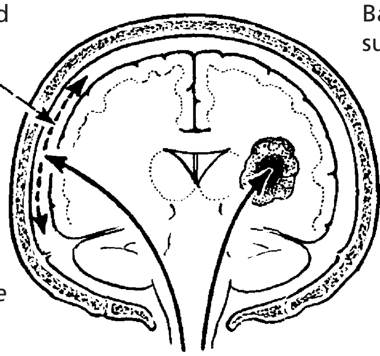
Infections will be considered in three broad aetiological groups:
(1) Bacterial, (2) Viral and (3) Miscellaneous types.

BACTERIAL INFECTIONS

1. **Most commonly by the blood stream**

Bacteria settling in subarachnoid space → **Meningitis**

Common organisms include:
Infants – *Escherichia coli*
Children – *Haemophilus influenzae*
Adults – *Neisseria meningitidis*
Elderly – *Streptococcus pneumoniae*

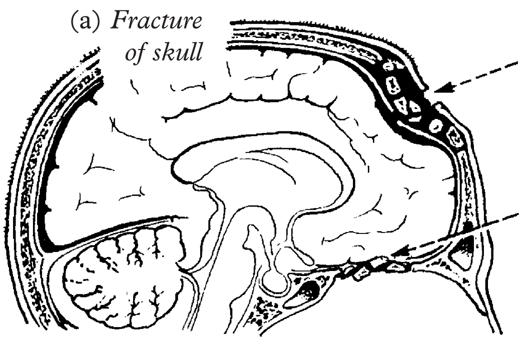


Bacteria settling in brain substance → **Brain abscess**

Common organisms include:
Streptococcus species
Staphylococcus aureus
Others

2. **From an adjacent local infected site** – these are pyogenic infections.

(a) *Fracture of skull*



Compound depressed fracture → Infection

Fracture of skull base leading into infected nasal sinus

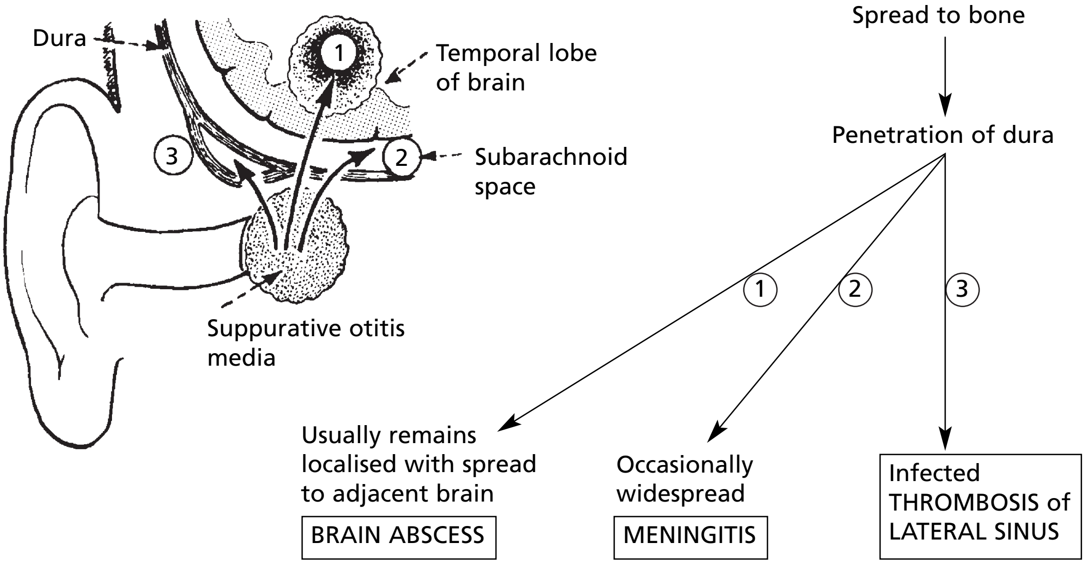
(1) Extradural abscess
(2) Subdural abscess (empyema)
(3) Meningitis

BACTERIAL INFECTION

Bacterial infections from an adjacent local infected site (*continued*)

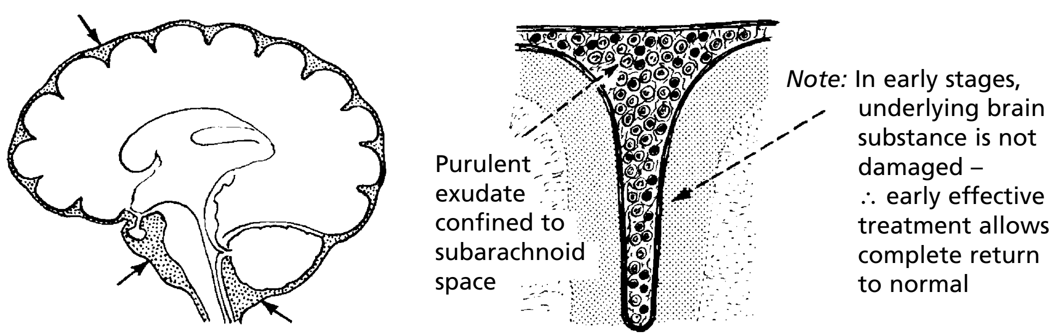
(b) *Middle ear and mastoid disease*

In untreated purulent otitis media, three serious complications may arise from spread of the inflammation.



PYOGENIC MENINGITIS

The whole subarachnoid space contains purulent exudate which is maximal in sulci and around the brain base cisternae.



In untreated or ineffectively treated patients who survive, complications include cranial nerve damage, hydrocephalus and variable brain damage.

The CSF in the acute stage contains neutrophils and the infecting organism can usually be demonstrated.

BACTERIAL INFECTION

PYOGENIC BRAIN ABSCESS

The abscesses resulting from direct spread of adjacent infection or by blood borne infection – as seen particularly in bronchiectasis – are often well circumscribed by a pyogenic membrane.

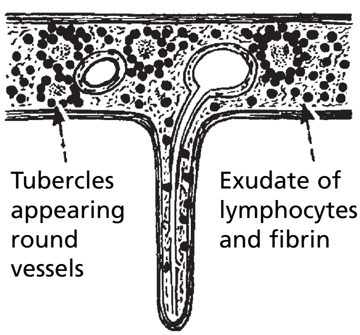
Sequels:
- HEALING with scarring → ± Functional loss or disturbance (including epilepsy)
- GRADUAL SPREAD
  - → Surrounding oedema → **Increased intracranial pressure**
  - → Rupture into ventricle or subarachnoid space → Meningitis

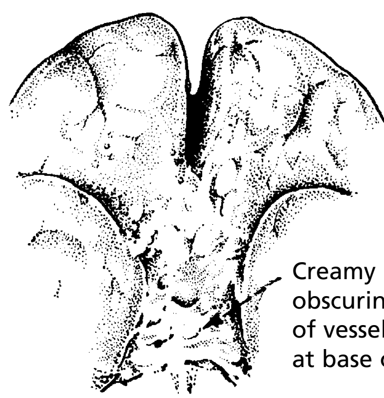
Clinical note: An abscess is often silent early in its evolution, and the infection at the site of entry may have healed before the onset of serious complications causes clinical signs.

Multiple small abscesses occur in staphylococcal pyaemia and microabscesses may complicate bacterial endocarditis. The cerebral pathology in these circumstances is only one facet of serious systemic infection.

TUBERCULOSIS

Infection of the nervous system is always secondary to disease elsewhere and may be a component of miliary tuberculosis. It may complicate AIDS and remains prevalent in many parts of the world. Without treatment tuberculous meningitis is invariably fatal.





TUBERCULOMA These localised tuberculous cerebral abscesses are now very rare.

SYPHILIS Neurological syphilis is rare nowadays. The main pathological lesions are described on p.76, 77.

VIRUS INFECTIONS

Compared with the incidence of virus infections in general, infection of the central nervous system is rare, even with viruses having an affinity for the CNS – **NEUROTROPIC VIRUSES.**

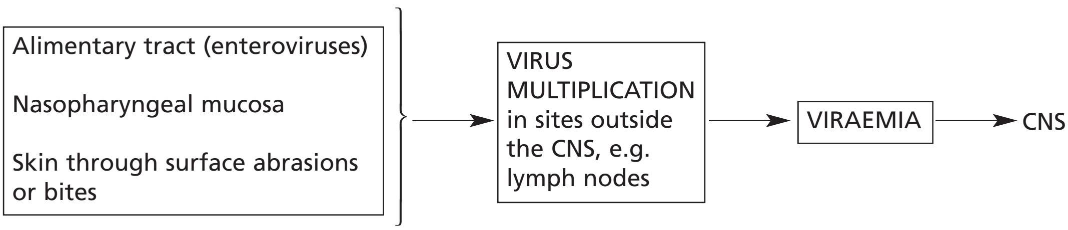
There are 3 broad groups:

1. **Acute**
   Cell lysis occurs towards the end of the viraemic phase of infection. This is the common type of disease. Herpes simplex, mumps, poliovirus and togaviruses are examples.
2. **Persistent**
   Viruses which usually cause damage outside the CNS behave uncharacteristically and cause continuing and active disease of the CNS over a long period (months – years). Measles, rubella and JC papovavirus are examples.
3. **Latent** virus infection is seen in herpes zoster and possibly plays a role in the demyelinating diseases.

Virus infection also has a possible role in oncogenesis within the CNS.

Routes of infection
Most viruses arrive at the CNS via the blood, but the factors which potentiate the establishment of disease within the CNS are poorly understood.

Primary portal of entry

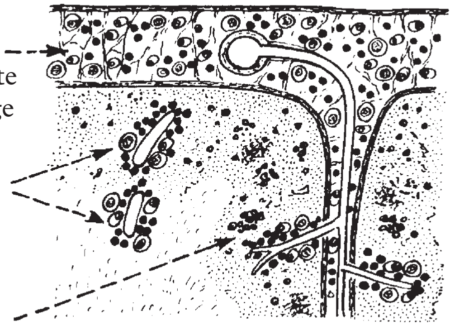


In rabies, the virus travels from the wound up the peripheral nerves to the CNS; a similar mechanism may be involved in herpes simplex encephalitis.

VIRUS INFECTIONS

BASIC PATHOLOGICAL EFFECTS

(a) **VIRAL MENINGITIS** is the commonest form of meningitis; the disease is usually mild and only the meninges are affected. Recovery is usually complete.
(b) In more severe cases, the brain substance is also damaged in varying degree – **ENCEPHALITIS** (meningoencephalitis).



The meninges (CSF) contain increased protein, normal sugar and a mononuclear cellular infiltrate (particularly **lymphocytes**, plasma cells and large mononuclear cells).
In the brain the characteristic changes are:

1. PERIVASCULAR CUFFING (same infiltrate as meninges)
2. ACUTE NEURONAL DAMAGE up to complete lysis with accompanying neuronophagia and inflammatory changes. In some conditions, surviving neurones contain cytoplasmic and/or nuclear inclusions. Specific viral inclusions, e.g. HSV and CMV, may be detected by immunohistochemistry.

To these basic changes, damage to myelin and glial tissue may be added, and small focal haemorrhages may be seen. The damage is effected in two ways:

1. By the direct effects of virus on cells.
2. By a host cell-mediated and humoral response to the infected cell.

Diagnosis
Examination of the CSF is helpful in establishing a diagnosis of aseptic meningitis or meningoencephalitis.
Note: The findings in tuberculous meningitis are very similar except that in tuberculous meningitis the CSF **sugar is low.**
The specific virus aetiology is more difficult to establish. PCR of CSF is useful for some viruses (esp. HSV). In severe cases brain biopsy may be required.

Clinical associations and progress
In viral meningitis, the illness is mild with fever, headache and neck stiffness the main signs. Recovery is almost always complete.

In meningoencephalitis, signs of cerebral 'irritation' and neuronal damage are seen, e.g. mental confusion, delusion, stupor, convulsions and coma, and there may be localising signs. In mild cases, recovery is complete, but in more severe cases residual paralysis and other signs indicative of permanent brain damage may follow. Death in coma with respiratory failure occurs in very severe cases.

VIRUS INFECTIONS

HERPES SIMPLEX VIRUS (HSV) ENCEPHALITIS

This is the commonest form of severe acute viral encephalitis and is almost always due to Herpes Simplex Virus Type 1. It occurs in 2 forms:

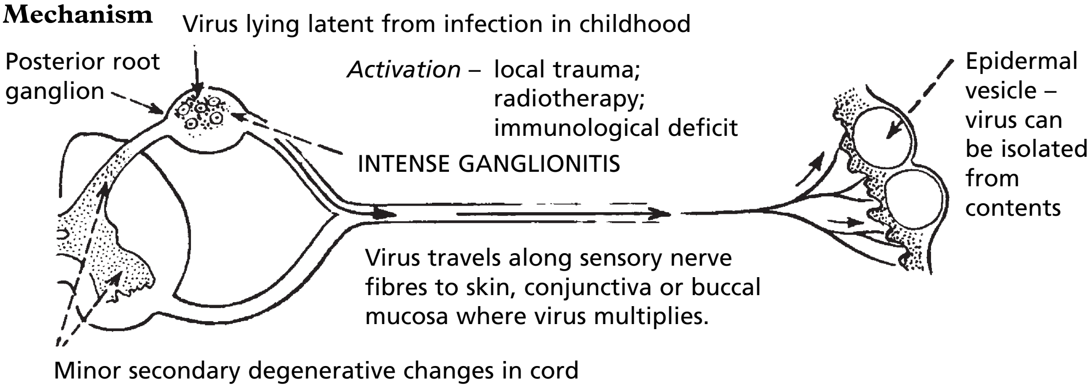
1. In infancy, as part of a generalised HSV infection.
2. In adults, due to reactivation of the virus in the trigeminal ganglion.

Most cases are sporadic but immunosuppression increases the risk.
The temporal lobes are most affected. Early treatment with antiviral drugs has now greatly reduced the previous high mortality.

HERPES ZOSTER (See also p.80)

This is a disease of adults, presenting as a painful vesicular rash, usually unilateral and affecting one or a few adjacent dermatomes only. It is due to recurrence of a latent varicella (chickenpox) infection.

Mechanism

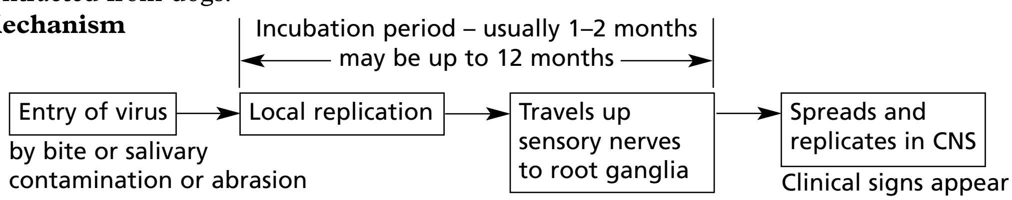


Sequels 1. An occasional sequel is intense pain with varying paraesthesiae and anaesthesia long after the acute phase has healed.
2. In cases of Vth nerve herpes, serious damage to the eye may result.

RABIES

The rabies virus shows marked neurotropism and can infect most mammals. Various wild carnivores (fox, jackal, skunk, vampire bats) are the natural reservoir. Many human cases are contracted from dogs.

Mechanism



An unremitting encephalitis particularly affecting the grey matter is established. Diagnostic Negri bodies (virus inclusions) are found at autopsy in the pyramidal cells of the hippocampus and the Purkinje cells of the cerebellum.
Clinically, the encephalitis presents with extreme excitation of the sensory system. The classical hydrophobia (fear of water) is due to serious disturbance of the swallowing mechanism with muscular spasm. Without supportive therapy death occurs and is due to respiratory muscle spasm or paralysis.

VIRUS INFECTIONS

ENTEROVIRUSES

These are small RNA viruses (picornavirus group) and include POLIOVIRUSES, COXSACKIE VIRUSES and ECHOVIRUSES.

Infection is acquired by ingestion of faecally contaminated material followed by proliferation in the intestine. In only a small minority of infected cases does the virus pass the blood-brain barrier and cause disease of the CNS.

In addition to aseptic meningitis, the POLIOVIRUSES (and very occasionally Coxsackie and Echo viruses) cause the classic paralytic disease, **ANTERIOR POLIOMYELITIS**. Vaccination has dramatically reduced the global incidence of poliomyelitis.

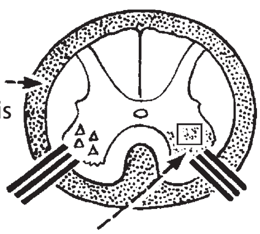
Pathological changes

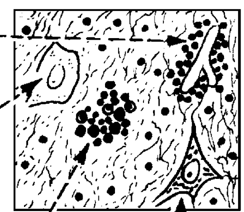
The pathological changes are reflected in three clinical stages: (1) acute, (2) recovery and (3) permanent residual disability.

(1) **Acute** (up to 2 weeks)

Febrile illness ------ Viraemia

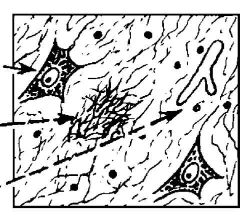
The virus shows tropism for motor nerve cells, particularly in the spinal cord



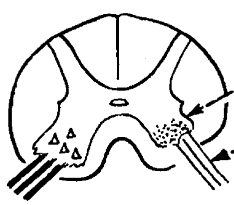


Sometimes RESPIRATORY paralysis ------ Damage to bulbar motor nuclei

(2) **Recovery**
(Several weeks/months)
Paralyses improve – in mild cases functional recovery may be complete



(3) **Permanent residual disability**
Wasting of muscles (neurogenic atrophy), varying deformities due to unopposed action of non-paralysed muscle



VIRUS INFECTIONS

PERSISTENT VIRUS INFECTIONS

Subacute sclerosing panencephalitis is a very rare disorder due to reactivation of latent measles virus. It affects children and young adults, often several years after uncomplicated measles, and is usually fatal within 6 months. The sequence is probably as follows:

Infection by measles virus ⟶ USUALLY FULL RECOVERY.
(usually under 1 year old)

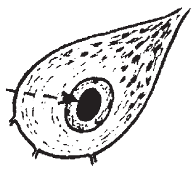
IN A VERY FEW INDIVIDUALS

↓

Persistent incomplete viral growth partially controlled by host defences continues over approx. 10 years despite high measles antibody titres.

↓

SUBACUTE ENCEPHALITIS ⟶ Numerous neurones contain nuclear inclusion bodies



↓

DEMENTIA ⟶ DEATH

A similar disorder may follow congenital rubella infection.

Progressive Multi-focal Leukoencephalopathy

JC papovavirus, a member of the polyoma virus group, may infect the oligodendrocytes of adults who are immunosuppressed. A rapidly progressive demyelinating disease follows – with degenerative changes in the deep white matter.

HIV and the Brain

Despite the introduction of highly active antiretroviral therapy (HAART), brain involvement is still a major cause of death in AIDS patients.

(a) HIV infection of the brain. This may lead to a subacute encephalitis often with dementia. The incidence has not decreased with HAART.
(b) Opportunistic infections including toxoplasma, fungi (cryptococcus), viruses (cytomegalovirus).
(c) Tumours – especially cerebral lymphoma.

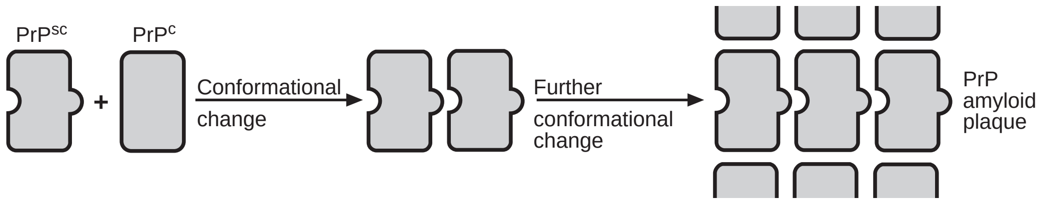
The incidence of (b) and (c) has decreased dramatically with HAART.

PRION DISEASES

Also known as the transmissible spongiform encephalopathies, this group of diseases is caused by abnormal, distorted PRIONS. A prion is a small protein molecule found in the brain cell membrane. Normal cellular prion protein is termed PrP^{c} whereas the distorted protein is termed PrP^{sc} (originally referring to scrapie but now a generic term).

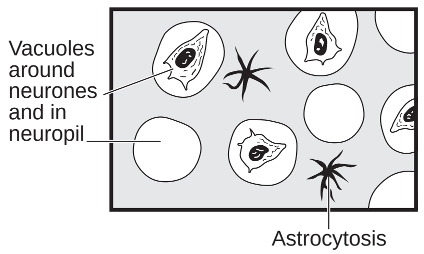
The PRION HYPOTHESIS

When a distorted prion molecule reaches the prions in the brain cell membrane of an individual, that molecule is able to act as a three-dimensional template to cause a normal prion molecule to adopt a similar distorted shape. This in turn can distort further proteins and so on.



PATHOLOGY

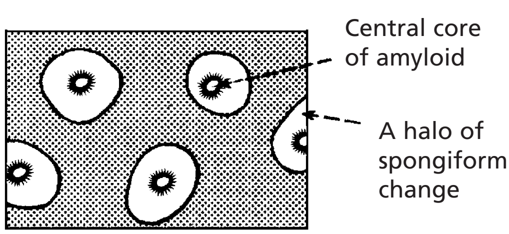
There are 4 characteristic histological features:



1. Spongiform change
2. Neuronal loss
3. Astrocytosis
4. Amyloid plaque formation. These are most frequently observed in the cerebellum. They can be detected by immunohistochemistry with antibodies to PrP^{sc}.

TYPES OF PRION DISEASE

1. **Creutzfeld–Jacob Disease (CJD)** – this may be: (i) **sporadic,** (ii) **acquired** through contact with infected material, e.g. pituitary derived hormones, corneal grafts or (iii) **familial** due a point mutation of the PrP gene. Spongiform change is the most consistent histological features. Plaques occur in around 10% of cases.



2. **Variant CJD** – This occurs in younger patients with early psychiatric symptoms and a longer clinical course. The strain of PrP responsible for vCJD is identical to a bovine spongiform encephalopathy (BSE) and is caused by ingestion of products from infected cattle. In contrast with CJD florid plaques are a histological hallmark. Also, unlike CJD, PrP may be detected in lymphoid tissue.
3. **Other** – includes KURU (historical) due to ingestion of human brain by cannibalism in New Guinea; GERSTMANN–STRAUSSLER–SCHEINKER disease; a familial dementia.

MISCELLANEOUS INFECTIONS AND INFESTATIONS

1. FUNGAL INFECTIONS

(a) **Primary infections.** In healthy adults, fungal infections are rare. Occasionally in the presence of heavy exposure to fungus, localised infection, often clinically insignificant, may occur, and in very rare cases CNS infection is a complication. In CRYPTOCOCCOSIS (C. *neoformans*), the fungus exhibits neurotropism and occasionally causes meningitis in otherwise healthy subjects.

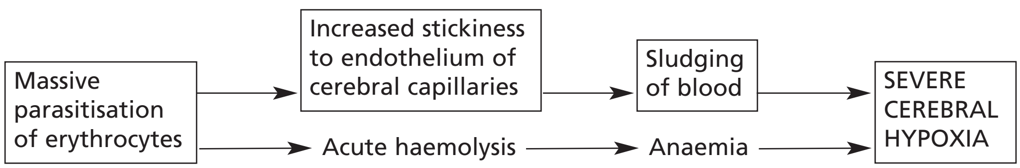
(b) **Opportunistic infections** are becoming more common nowadays due to the use of immunosuppressive therapy and the increasing prevalence of AIDS. Various fungi including *Candida, Aspergillus, Nocardia* may cause serious cerebral damage. The incidence is decreasing in AIDS patients due to HAART.

2. PROTOZOAL INFECTIONS

(a) CEREBRAL MALARIA

Cerebral complications may occur in the severe acute malaria (falciparum type) which affects non-immune adults. Clinically, coma rapidly proceeds to death.

Mechanism



At autopsy the brain is swollen (oedema) and there may be petechial haemorrhages. Histologically, the capillaries are congested and malarial parasites and pigment are easily seen.



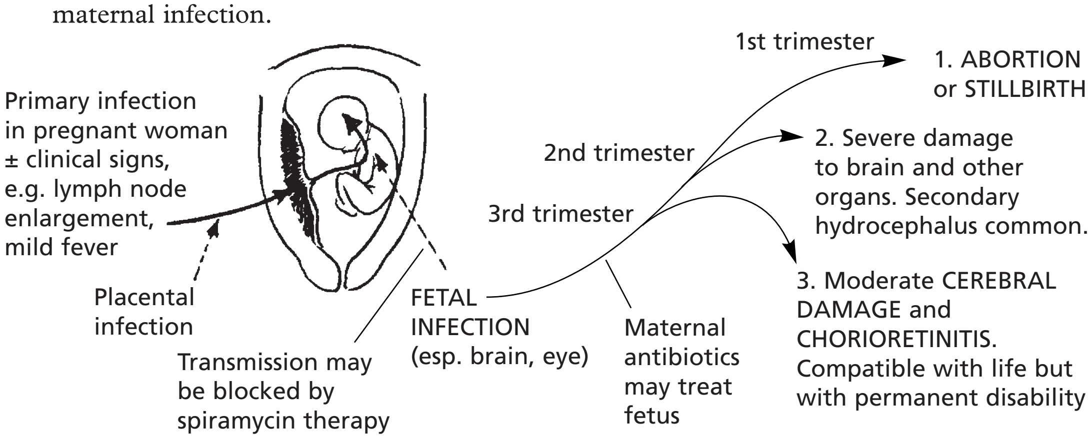
MISCELLANEOUS INFECTIONS AND INFESTATIONS

Protozoal infections (*continued*)

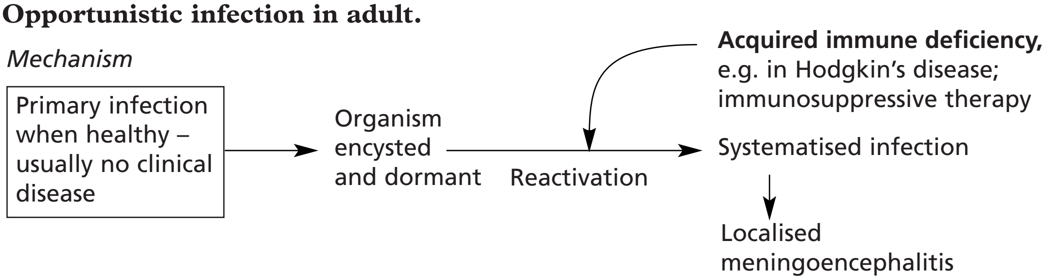
(b) **TOXOPLASMOSIS**

Although infection by *T. gondii* is common, serious nervous tissue damage is rare and is seen in two main circumstances. In both, it occurs as part of a systemic infection.

(i) In **congenital toxoplasmosis**, the infection is acquired by the fetus during a primary maternal infection.

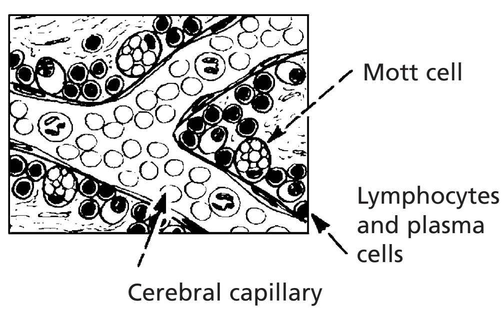


(ii) **Opportunistic infection in adult.**



(c) **TRYPANOSOMIASIS (AFRICAN SLEEPING SICKNESS)**

T. brucei infection is transmitted to humans from animal reservoirs by the Tsetse fly. The organism is neurotropic and a meningoencephalitis results. The infection is associated with excessive IgM production in CSF. The 'cuffing' infiltrate has a high component of plasma cells and also 'Mott' cells – plasma cells distended by eosinophilic globules (denatured Ig).



3. **METAZOAL INFESTATION**

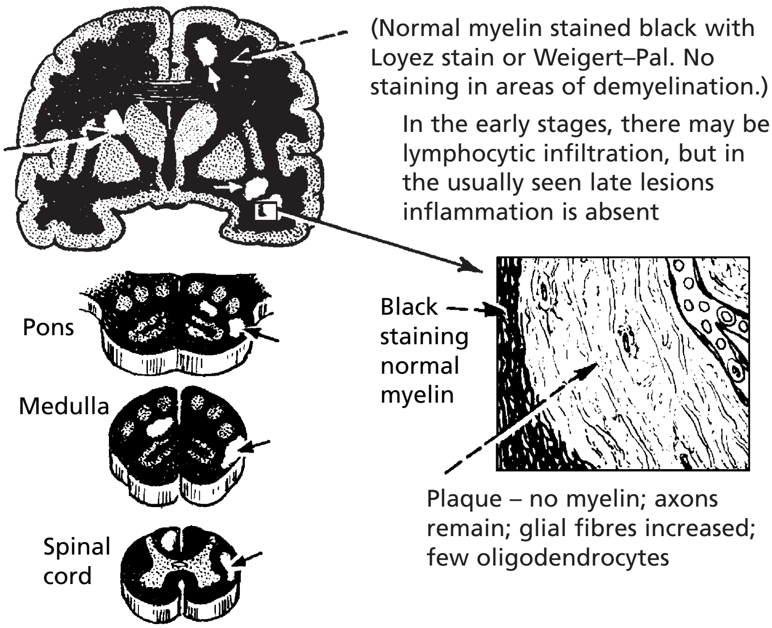
Cysticercosis.
The larvae of *Taenia solium* may encyst in the brain and can be the cause of epilepsy.
Hydatid cyst – also occurs in the brain (see p.360).

DEMYELINATING DISEASES

MULTIPLE SCLEROSIS (MS)

This is the commonest demyelinating disease – where the myelin sheath breaks down, leaving the axons healthy but with serious effects on their function.
Multiple sclerosis is a chronic disease of young adults.

The basic pathological change is a scattering of 'plaques' of demyelination most commonly adjacent to the lateral ventricles, optic nerve and chiasm, brainstem, cerebellum and spinal cord.



Clinical associations
The neurological signs reflect *white matter damage* – upper motor neurone weakness and paralysis; incoordination; visual disturbances; paraesthesia. ('Grey matter' signs, e.g. aphasia, fits and muscle atrophy are rare.)

Course of disease	*Onset* Often acute; may be unnoticed.	*Progress over many years* Remission . . . Relapse . . . Remission → Incremental deterioration → Death

Variants are:
1. acute severe disease – rapid progress to death
2. chronic progression without remission
3. minimal signs with very long remissions.

Aetiology – This is unknown.
Geographically, the disease is common throughout temperate Europe and North America and is rare in the tropics.
A possible mechanism is:

LATENT VIRAL INFECTION
(? measles, ? EBV, ? Herpes)

GENETIC DISPOSITION
(High concordance in identical twins)
increase in HLA A3, B7, DW2, DR2

↓

Activation of CD4+ T cells

↓

Autoimmune attack on myelin

↓

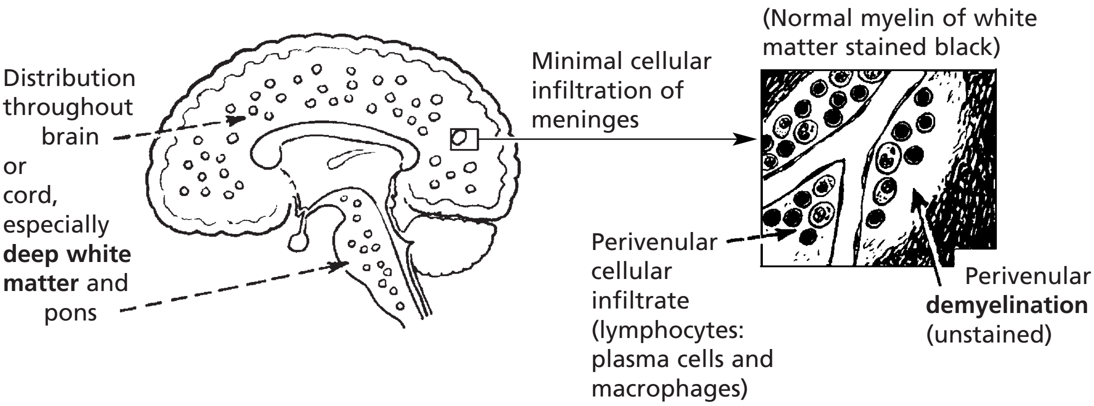
DEMYELINATION

DEMYELINATING DISEASES

ACUTE DISSEMINATED ENCEPHALOMYELITIS

An acute encephalitis in which demyelination is a prominent and characteristic feature is a very rare sequel to many natural viral diseases such as mumps, measles, chickenpox and rubella and to vaccination, historically against smallpox and rabies.

Clinically, there is fever, headache, vomiting and drowsiness followed by coma. There may be clinical evidence of focal neurological damage. Pathological changes are widespread in the brain and cord and rapidly progressive.



In **ACUTE HAEMORRHAGIC LEUKOENCEPHALITIS**, to these are added actual petechial haemorrhages from damaged vessels, particularly in the white matter; not all cases follow virus infection.

Mechanism. It is thought that in these disorders the damage to the myelin is not the result of direct virus attack but is an *autoimmune* reaction in which the antigen is a component of myelin and the virus in some unknown way acts as a trigger.

DISEASES due to ABNORMAL MYELIN

In this group of rare 'leukodystrophies', the molecular structure of myelin is abnormal due usually to abnormal or deficient enzyme action. Most cases are genetically determined, present in early life and progress fairly rapidly.

Abnormal metabolites which can be specifically identified accumulate in macrophages, glial cells and sometimes neurones.

e.g. 1. In **metachromatic leukodystrophy**, the accumulation of a *sulphatide* gives a metachromatic staining reaction and characteristic EM appearance.

2. In **Krabbe's disease** there are typical multinucleated histiocytes (called globoid cells) containing *cerebroside*.

PARKINSON'S DISEASE

This is a disease of the extrapyramidal system which links the higher motor centres and effector motor cells of the spinal cord. Important neurotransmitters are DOPAMINE and γ-aminobutyric acid (GABA).

Aetiology – The disease occurs in 2 main circumstances:

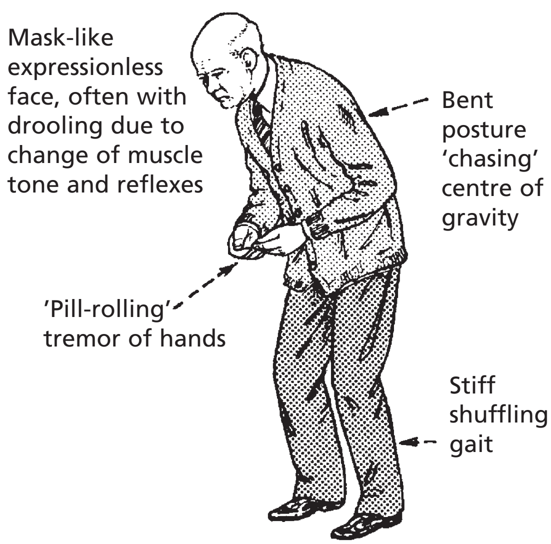
(a) ***Idiopathic:*** The majority of cases occurring in the elderly population (1% of over 60s) are idiopathic and the cause remains unclear. Genetic and environmental factors may be involved.

Genetic: There is a 2–3 times increased risk of the development of Parkinson's disease in the first-degree relatives of patients.

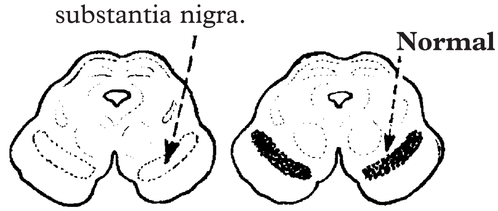
Environmental: Some pesticides can cross the blood–brain barrier and may be associated with Parkinson's disease.

(b) ***Secondary:***
1. **Postencephalitic** (historically) i.e. as a sequel to encephalitis lethargica which occurred in epidemic form in the 1920s.
2. **Drug induced.** The use of neuroleptic drugs may induce the syndrome temporarily (occasionally permanently), by disturbing the balance of the chemical transmitters.
3. **Arteriopathy.**
4. **Heavy metal poisoning.**

Clinically, **Parkinsonism** illustrates the classical features of extrapyramidal damage.



Pathological mechanism
In all cases of long-standing Parkinsonism of any type, degenerative changes are seen in the extrapyramidal nuclei. In particular, there is depigmentation of the substantia nigra.



Also there is a deficiency of DOPAMINE in affected nuclei.

Histologically, there is loss of neurones, and the surviving nerve cells contain inclusions known as Lewy bodies (p.546).
Other extrapyramidal disorders include the choreas, of which there are 2 main types. Sydenham's chorea occurs in children with rheumatic fever, while chorea is a manifestation in some patients with Huntington's disease.

MISCELLANEOUS DISORDERS

NUTRITIONAL AND METABOLIC DISORDERS (ENCEPHALOPATHIES)

In the last analysis, all disorders in this group are mediated by disturbed neuronal metabolism, so that exact classification may present some difficulty. However, it is convenient to consider them in 2 broad groups.

1. NUTRITIONAL DEFICIENCY

The vitamins of the B group are important coenzymes in several intracellular oxidative pathways. Deficiency, which may arise from primary malnutrition but more commonly in association with alcohol abuse, is the cause of degenerations of the brain, spinal cord and peripheral nerves.

Wernicke's encephalopathy

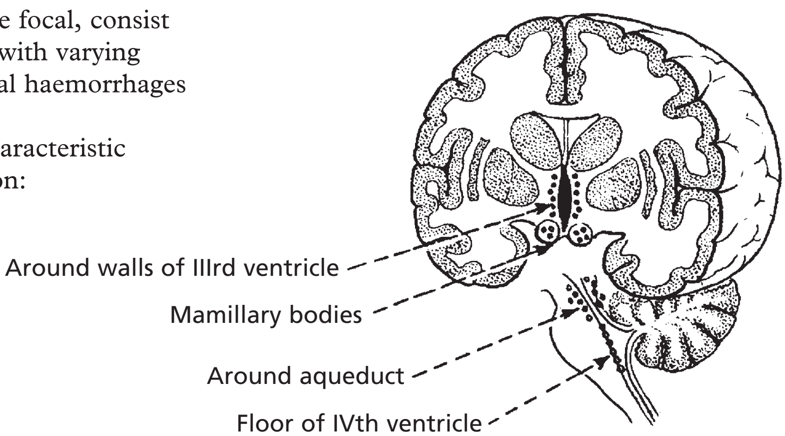
Clinically, this condition presents with disturbances of consciousness, ataxia and visual disturbances, and without prompt treatment progresses to death in coma.
In Western countries, chronic alcoholism is usually present; often a particularly heavy bout of drinking precipitates the condition.

Chronic alcoholism ⟶ Poor diet ⟶ NUTRITIONAL DEFICIENCY of vit B complex, esp. THIAMIN.

Bout of heavy drinking ⟶ Vomiting —Accentuates⟶ (NUTRITIONAL DEFICIENCY)

The blood PYRUVATE level is raised.

The lesions, which are focal, consist of glial proliferations with varying neurone loss. Petechial haemorrhages may be seen.
The lesions have a characteristic anatomical distribution:



Prompt treatment with thiamin minimises the damage, but if treatment is omitted or delayed, permanent damage results. The patient may have a persistent Korsakoff's psychosis. At autopsy, there is visible shrinkage of the mamillary bodies.

MISCELLANEOUS DISORDERS

2. METABOLIC DISORDERS

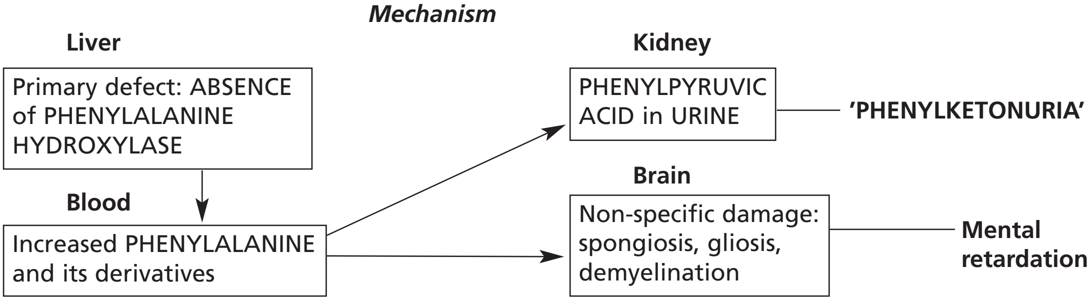
In the following examples, the metabolic defect causes neurological disorder, but in addition, other organs are seriously disturbed.

(a) ***Aminoacidopathies***
A wide variety of hepatic enzyme defects in the complex metabolism of amino acids has now been described. When neurological damage occurs, it is essentially non-specific and developing in the immediate postnatal period, a critical time in the development of the brain which leads to ***mental retardation.***

Phenylketonuria is an example.

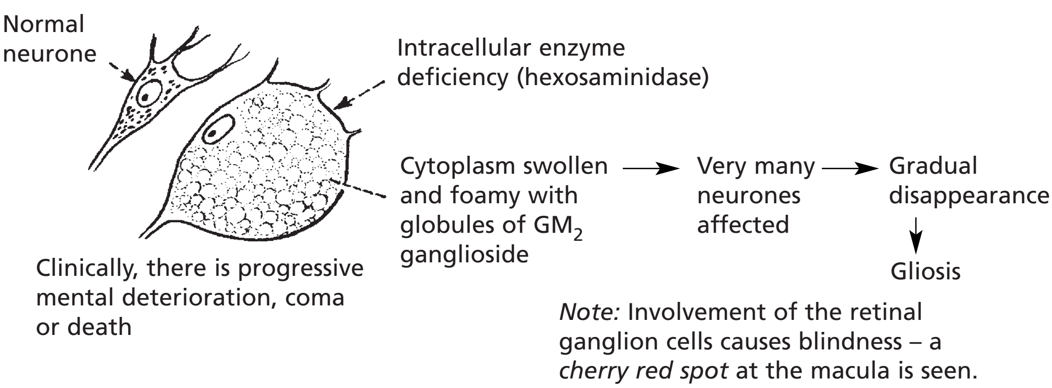
The importance of this disease is that the effects can be prevented by dietary restriction of phenylalanine-containing substances, provided the treatment is begun within 60 days of birth.

Mechanism



(b) In the ***neuronal storage diseases***, which usually present during the first decade, deficiency of lysozomal enzymes leads to accumulation of intermediate metabolites in the neurones. The diagnosis of the condition often depends on the identification of the abnormal metabolite by histochemistry or EM.

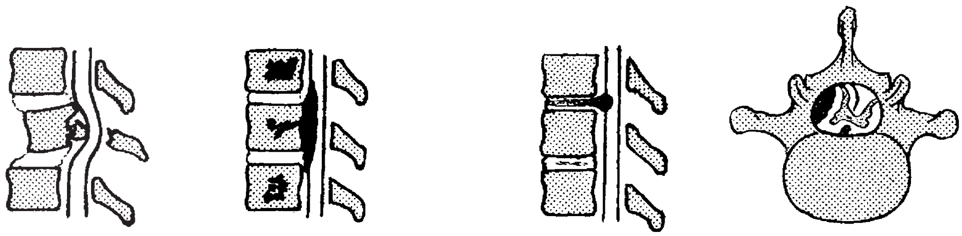
Tay–Sach's disease (amaurotic familial idiocy) is an illustrative example.



In these disorders, other organs may be mildly affected by the enzyme defect but the neurological effects are predominant.

DISEASES OF THE SPINAL CORD

In purely spinal lesions, basic disease processes have important anatomical and functional implications. Lack of space for expansion produces important compression effects. Examples are:



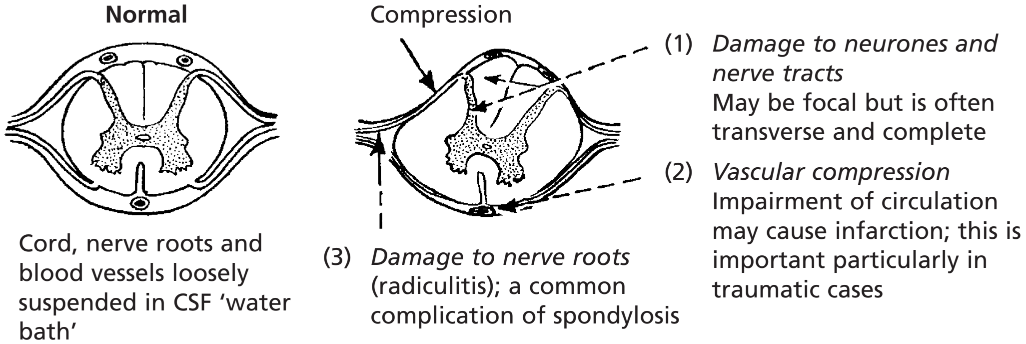
Fracture/ dislocation of vertebra

Tumour (usually secondary) in vertebrae growing into canal

Prolapse of intervertebral disc

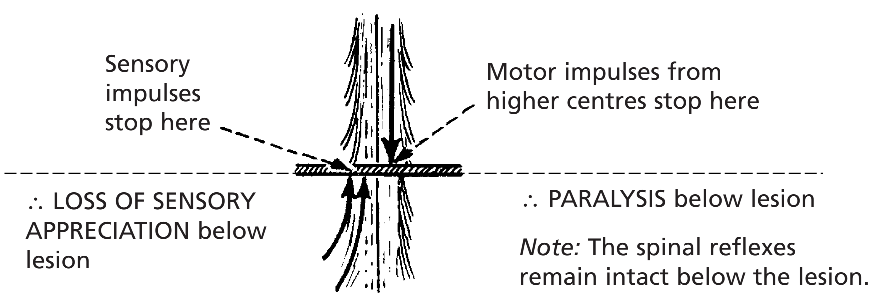
Tumour of meninges or nerve sheath

Effects



At the level of the lesion, there is loss of the sensory and motor connections which constitute the spinal reflex.

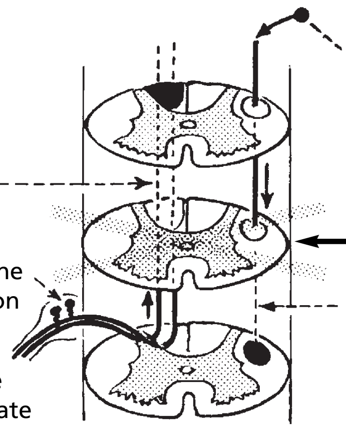
In addition, severance of the longitudinal tracts cuts off the cerebral connections to all parts below the lesion.



DISEASES OF THE SPINAL CORD

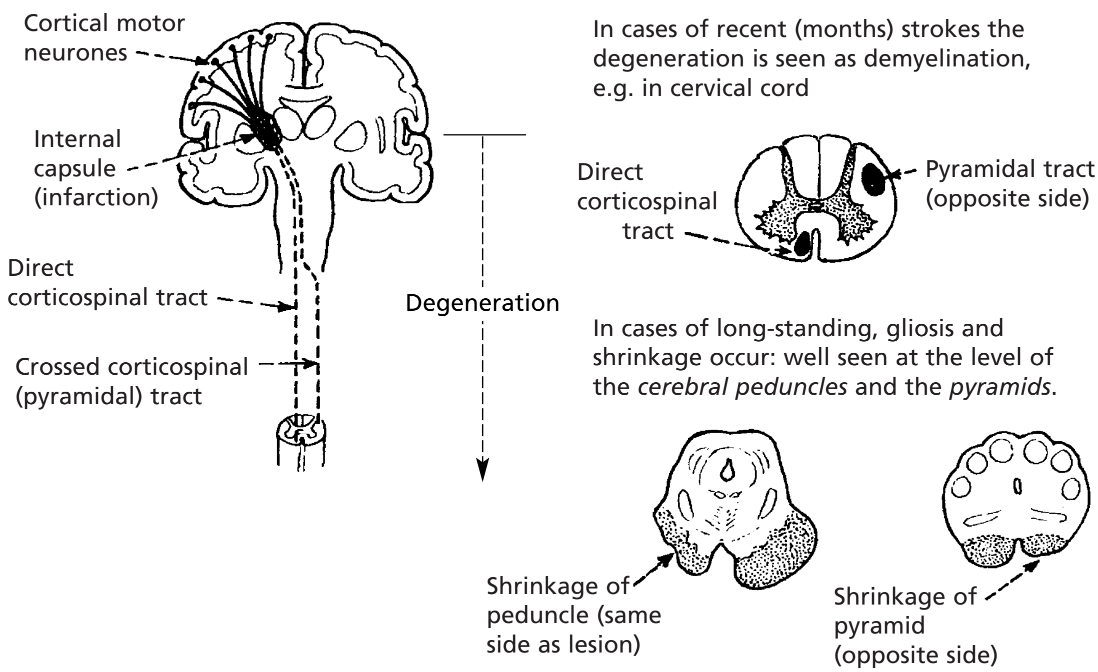
ASCENDING AND DESCENDING DEGENERATIONS

The long tract fibres which are cut off from their neurones progressively degenerate.



Note: In transverse lesions of the cord, all the long tracts degenerate either upwards (sensory) or downwards (motor). These particular tracts are shown for illustrative convenience.

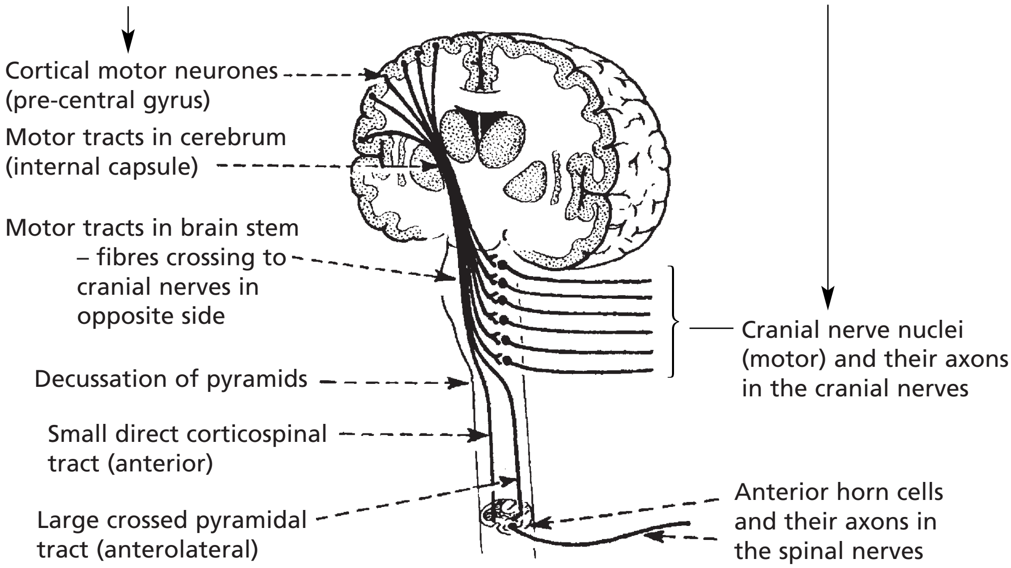
The commonest example of **descending degeneration** is seen following cerebral infarction involving the internal capsule; the degeneration extends from the lesion along the corticospinal axons to their terminations in the anterior horn.



DISORDERS OF MOTOR PATHWAYS

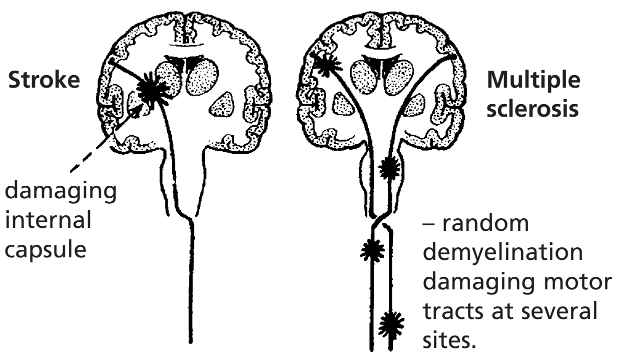
The concept of upper and lower motor neuronal activity, based on anatomical and physiological evidence, has great clinical value in diagnosis.

The **upper motor neurones** (UMN) synapse with the l**ower motor neurones** (LMN)



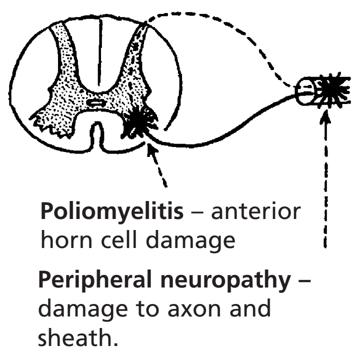
It will be appreciated that in its long course from the cerebral cortex to the anterior horn, the upper motor neurone is susceptible to damage from a variety of disease processes acting at various sites. The lower motor neurone may be damaged in the cord or in the peripheral nerve. Important illustrative examples are:

Upper motor neurone damage



Note: Clinically, tendon jerks are increased and the plantar reflex is extensor.

Lower motor neurone damage



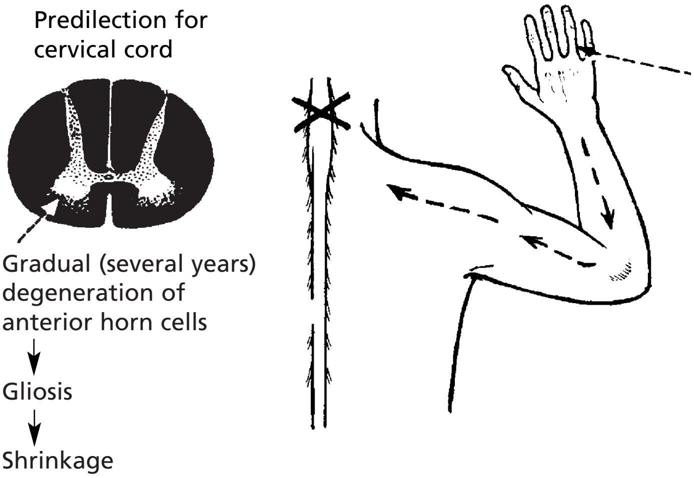
Reflexes are absent and muscles atrophy.

MOTOR NEURONE DISEASE

This is a disease of unknown aetiology occurring predominantly in adult males. In a few cases motor neurone disease is familial and is caused by a mutation in the gene encoding a free radical scavenger, superoxide dismutase 1. Other susceptiblity genes have been identified.

Three variants of MND are recognised according to the distribution of the disease process.

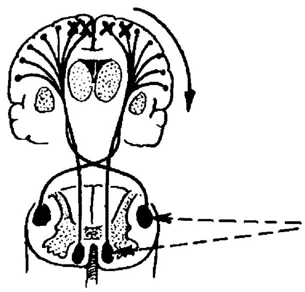
1. In **progressive muscular atrophy**, as the name implies, the main signs are of neurogenic atrophy due to degeneration of the anterior horn cells (LMN).



Sites particularly affected are:

1. Small muscles of hand – wasting ('simian hand')
   Note: While degeneration of neurones is proceeding spontaneous irregular discharges cause muscle twitching –
   FASCICULATION
2. Muscles of arm and shoulder girdle.
3. Spread towards medulla.
4. Later leg weakness and paralysis reflect both LMN and UMN damage.

2. In **amyotrophic lateral sclerosis** there is both UMN and LMN damage: 'lateral sclerosis' indicates the degeneration of the pyramidal tracts.



The degeneration affects the cortical motor cells – particularly those supplying the lower limbs but spreading over a few years to involve the neck and head centres. Voluntary movements of the face, jaw and tongue muscles are defective.
Corticospinal tracts showing degeneration and, later, gliosis.

The lesions are very rarely pure UMN type even initially, and with progression, the LMN lesions increase.

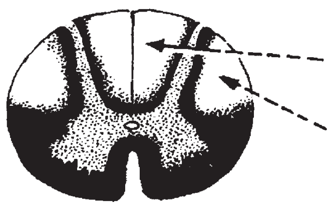
3. **Progressive bulbar palsy**
   In a few cases, the disease begins with signs of cranial nerve dysfunction – swallowing and facial movements are impaired.

Progress
In motor neurone disease after a long progressive illness the stage is reached when the bulbar degeneration is severe enough to prevent elimination of secretions from the respiratory tract. Death is usually due to aspiration bronchopneumonia or respiratory failure.

MIXED MOTOR AND SENSORY DISORDERS

SUBACUTE COMBINED DEGENERATION OF CORD

Due specifically to vit B_{12} deficiency. If replacement therapy is begun early enough, there is restoration to normal.

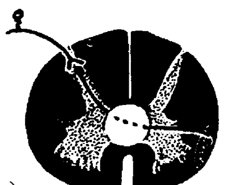


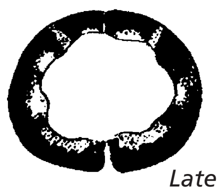
Degenerated tracts		Effects
1. Posterior columns	→	Sensory loss (vibration and proprioception): ataxia
2. Corticospinal tracts	→	Upper motor neurone damage – spastic paralysis

SYRINGOMYELIA

In this condition, a glial-lined cystic space gradually expands within the cord, usually in the cervical region. The pathogenesis is not certain, but it is suggested that the lesion is essentially an expansion of the central canal associated with a mild developmental abnormality of the distal end of the IVth ventricle. Some cases follow spinal trauma.

Effects
Damage to sensory fibres decussating in the cord. Loss of temperature and touch in local segments (**dissociated anaesthesia**).





Destruction of grey matter and gradual affection of long tracts. Loss of local reflexes. Severe sensory loss. Spastic paralysis.

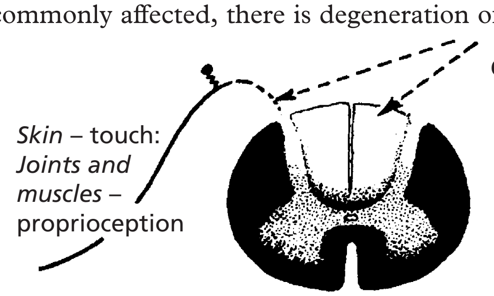
SPINOCEREBELLAR DEGENERATIONS

This is a large group of related disorders, usually familial, in which there is motor and sensory degeneration particularly affecting gait, posture, equilibrium and movement. There is sometimes optic nerve and retinal damage and intellectual disturbance.

Friedreich's ataxia is the most common hereditary ataxia and is caused by expansion of a trinucleotide triplet repeat in the FRATAXIN gene on chromosome 9. Deficiency of frataxin leads to mitochondrial respiratory chain dysfunction. In addition to the effects of spinocerebellar degeneration there may be cardiomyopathy with arrhythmia.

SENSORY DISORDERS

In **TABES DORSALIS**, a tertiary manifestation of syphilis in which the lumbar cord is commonly affected, there is degeneration of the posterior nerve roots and columns.



Clinically
Loss of vibration sense and reflexes
Ataxia
Trophic skin ulcers
Severe joint derangement (Charcot, p.602)

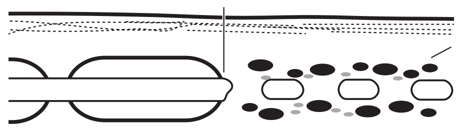
Additional features
Cranial and sympathetic nerve involvement – disturbance of pupillary reflex

Painful visceral crises

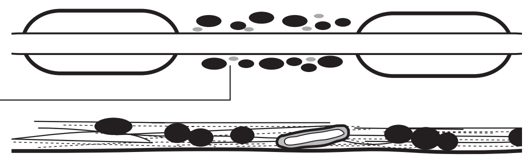
THE PERIPHERAL NERVES/THE NEUROPATHIES

There are 3 main reactions that occur in peripheral nerves.

1. Traumatic damage followed by regeneration or formation of a traumatic neuroma.
2. Damage to axons and myelin sheath.
   (a) Axonal degeneration



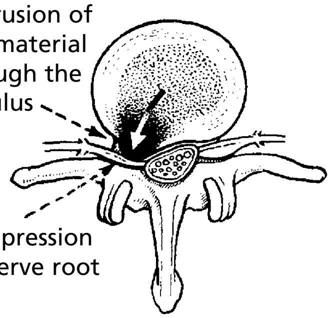
   (b) Demyelination

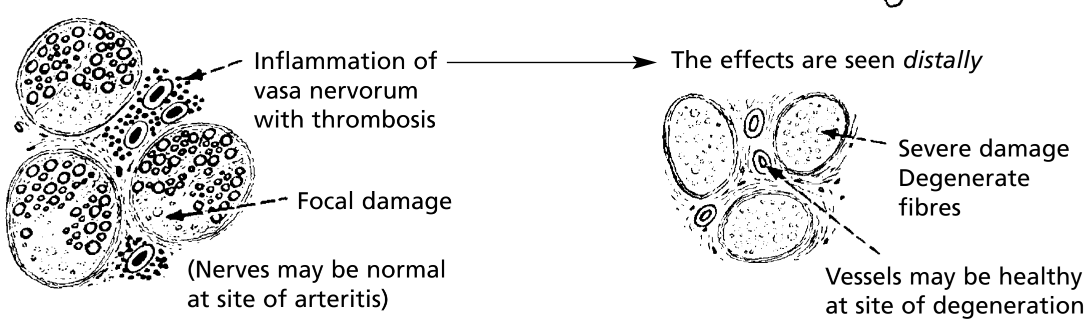


3. Damage to supporting structures, e.g blood vessels or epi-, peri- or endoneurium.

CLINICAL MANIFESTATIONS OF PERIPHERAL NERVE DISORDERS

1. ***Mononeuropathy:*** single nerve damage by compression, e.g. compression of median nerve in carpal tunnel syndrome, compression of nerve root by prolapsed intervertebral disc
2. ***Mononeuritis multiplex:*** where several nerves are involved, e.g. arteritis with inflammation of vasa nervorum leading to ischaemia





THE NEUROPATHIES

3. ***Polyneuropathy***: where there is extensive and symmetrical disturbance of function, often peripheral in distribution and especially affecting the legs. There are many causes:

   Toxic – diphtheria; lead; arsenic; drugs used in medicine.

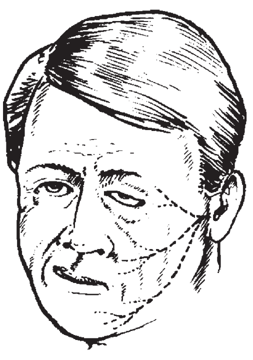
   Deficiency states – particularly vit B complex deficiency causing Beri-Beri.

   Metabolic disorders – diabetes mellitus; porphyria, metachromatic leukodystrophy, associated with malignant tumours, in uraemia treated by dialysis.

   Inflammatory/Immunological – Guillain–Barré syndrome where ascending paralysis occurs usually after a mild febrile illness. Respiratory failure requires supportive treatment but recovery is usually complete.

Other Neuropathies

Bell's Palsy
This is a unilateral facial weakness of sudden onset. The cause is unclear but it may occur with draughts and chilling and is not uncommon in pregnancy. The mechanism is thought to be inflammation with swelling and compression of the facial nerve in its course in the bone adjacent to the internal auditory meatus. Progress: 75% of cases recover in about 4–8 weeks.



Note drooping and loss of facial expression on paralysed side.
Facial muscles pull across the mid line – mouth is distorted.

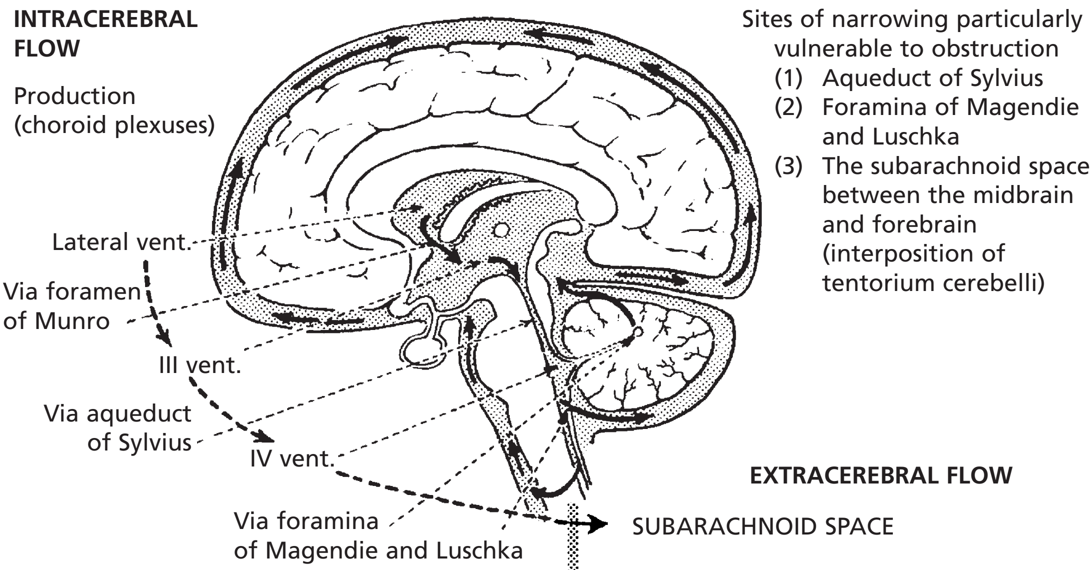
Leprosy
In the lepromatous form, there is a diffuse neuropathy involving the peripheries (which are at the lower temperature required for proliferation of *M. leprae*).

There is a low grade chronic inflammation of the nerve sheaths associated with fibrosis and nerve fibre degeneration.

HYDROCEPHALUS

In hydrocephalus, the volume of the CSF is increased and the ventricles are dilated. In the majority of cases, there is an increase in intracranial pressure. Three possible **mechanisms** are considered.

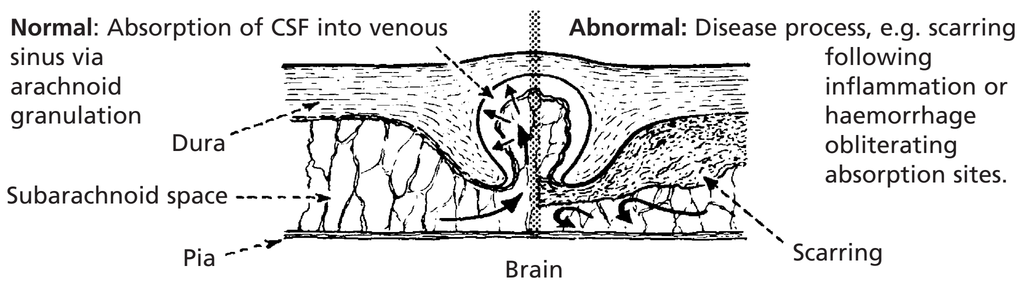
1. **Overproduction of CSF**
   The choroid plexus will secrete more CSF to compensate for any external leak, but overproduction is not a cause of hydrocephalus.
2. **Obstruction to the flow of CSF is the common mechanism.**



In cases of obstruction up to the IV ventricular foramina, the CSF cannot reach the subarachnoid space; e.g. sites 1 and 2. The hydrocephalus is **NON-COMMUNICATING.**

When the obstruction is beyond the foramina, e.g. site 3, the hydrocephalus is **COMMUNICATING.**

3. **Defective absorption of CSF** is a rare mechanism.



HYDROCEPHALUS

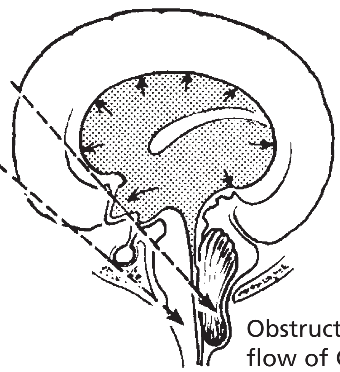
CAUSES

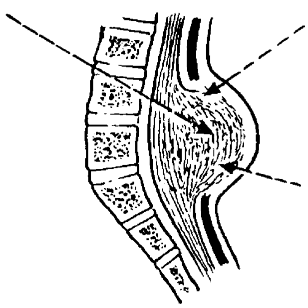
The diseases causing hydrocephalus fall into two groups:

1. **Congenital (developmental) abnormalities**

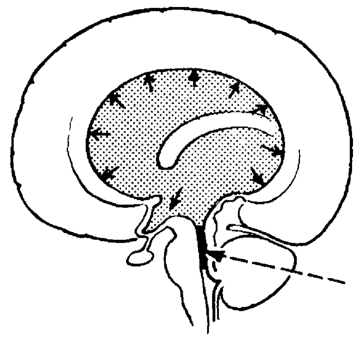
The common conditions are:

(a) ***The Arnold–Chiari malformation***

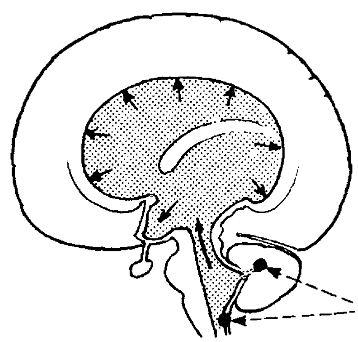




(b) ***Congenital stenosis or atresia of aqueduct of Sylvius***



(c) ***Atresia of foramina of Magendie and Luschka***



2. **Acquired hydrocephalus**

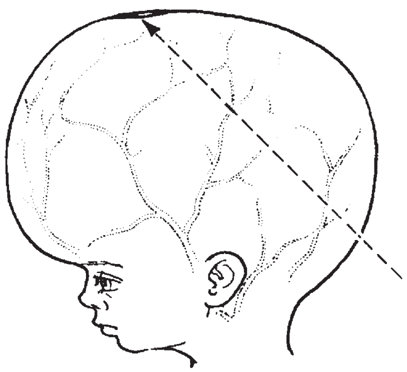
Of the many possible conditions causing hydrocephalus, the following are most common: (a) cerebral tumour (primary or secondary) and (b) scarring of the meninges following meningitis or subarachnoid haemorrhage.

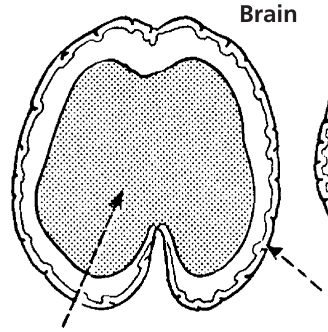
As already explained, whether any particular disease produces hydrocephalus depends largely on the site affected.

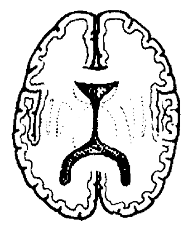
HYDROCEPHALUS

EFFECTS

In the infant and young child, the pliable skull expands to accommodate the enlarging brain – but these extreme changes do not occur if an effective shunt is inserted.



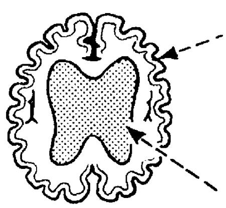


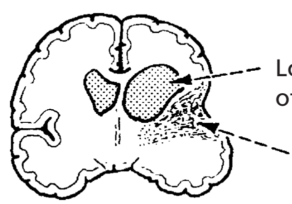


In the **older child and adult**, enlargement of the brain is prevented by the inability of the skull to expand. The main change is dilatation of the ventricles associated with the effects on the brain of increased intracranial pressure.

SPECIAL TYPES OF HYDROCEPHALUS

1. In cases of generalised cerebral atrophy, the ventricular system enlarges to compensate for the loss of cerebral tissue. This also happens locally when cerebral tissue is lost, e.g. following infarction.





No increase in pressure is involved and the pathological and clinical effects wholly reflect the primary loss of cerebral tissue. The condition is sometimes called **secondary hydrocephalus.**

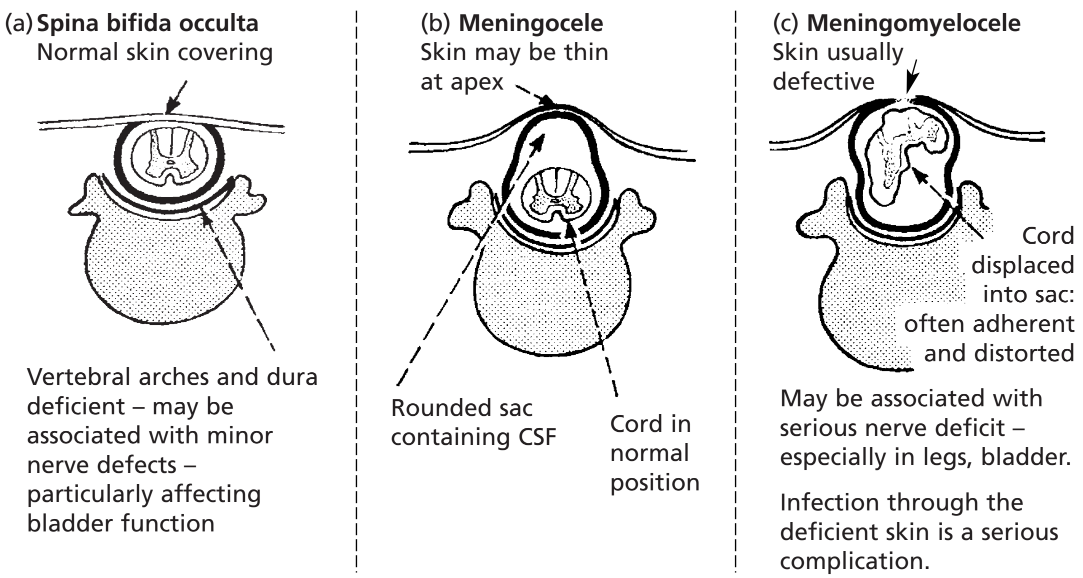
2. **Normal pressure hydrocephalus**

In this rare condition, progressive mental deterioration (dementia) and disturbances of gait and micturition are associated with ventricular dilatation. CSF pressures are usually at the high end of the normal range. The exact mechanism is not understood but it is thought to be a form of communicating hydrocephalus with unpaired CSF reabsorption at the arachnoid granulations. The diagnosis has assumed importance because in some cases CSF shunt procedures have arrested the progress. The aetiology is obscure.

DEVELOPMENTAL ABNORMALITIES

Developmental abnormalities of the brain and cranium are relatively common. They range from anencephaly (absence of brain) to minor malformations, e.g. meningocele and encephalocele. There may be associated congenital defects elsewhere in the body.

Neural Tube Defects
Local defects in the development and closure of the neural tube are common and largely preventable by folic acid supplementation in pregnancy. They include:

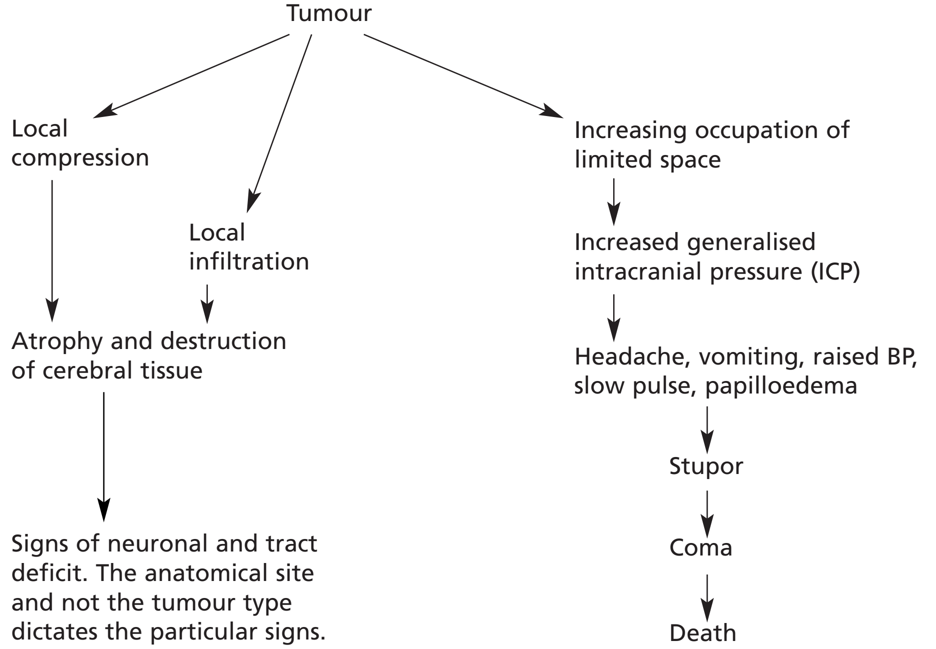


Diagnosis in utero
α-fetoprotein leaks through the defective skin covering and increased amounts are found in the amniotic fluid and in maternal blood. Ultrasonography may also reveal the defect.

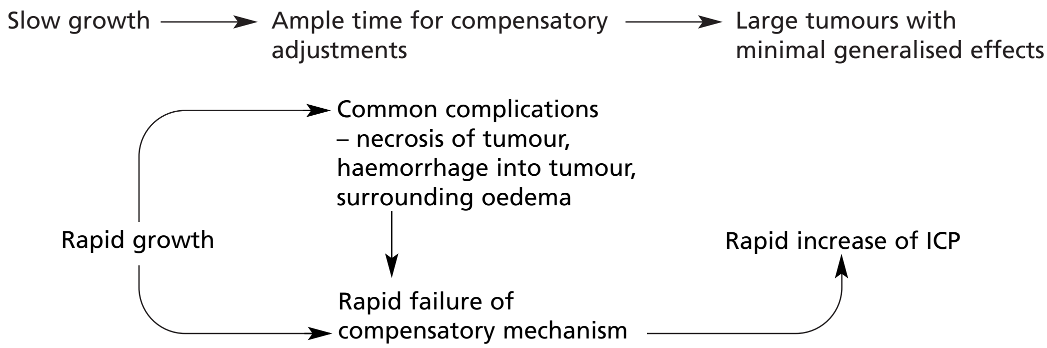
Complications
In addition to severe neurological deficits which are aggravated by infection, an important complication even in minor defects is **HYDROCEPHALUS** due to an association with the Arnold-Chiari Malformation (p.571).

TUMOURS OF THE NERVOUS SYSTEM

The following scheme illustrates the various non-specific clinicopathological effects of a tumour within the skull.



An important factor which materially influences the relative importance of each of these effects is the rate of tumour growth.



Tumours will be considered in a simplified form under the following broad headings:

1. Secondary neoplasms.
2. Neoplasms of neuroectodermal origin.
3. Neoplasms arising in supporting tissue (mesodermal).
4. Neoplasms and swellings of developmental origin.
5. Neoplasms of nerve sheaths.

SECONDARY BRAIN TUMOURS

In the general population the incidence of metastatic cerebral tumour is much higher than that of primary cerebral neoplasm. The two most common primary sites are lung and breast, but any malignant tumour can metastasise to the brain.

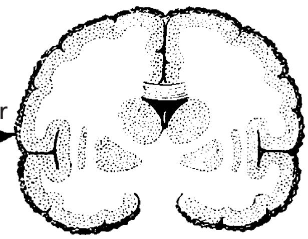
The common presentation is in the form of multiple, well-delineated spherical nodules, randomly distributed



Only occasionally is there a single nodule.

A less common distribution is by permeation of the subarachnoid space – **meningeal carcinomatosis.**

Brain surface covered by a layer of tumour tissue



Carcinoma, leukaemia and lymphoreticular neoplasms may spread in this way (malignant cells may be seen in the CSF).

Secondary tumours may cause serious spinal damage by destroying the integrity of the vertebrae although the vertebral discs usually remain intact (cf. spinal TB). The prostate and cervix, in addition to lung, breast and kidney, are usual primary sites.

In contrast to tumours causing neurological damage by their physical presence and growth, less commonly *non-metastatic effects of cancer* are seen.

There is a wide range of disorders which are conveniently divided into two groups:

1. Neurological disorders in which the mechanism and association with cancer are known:

Examples	**Mechanism caused by cancer**
Opportunistic infections	Immune depression
Metabolic and hormonal imbalance	Destruction of organs, e.g. liver, kidney Inappropriate secretion
Vascular accidents	Coagulation disorders

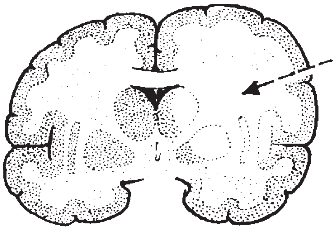
2. A group of conditions in which the mechanism is not known. This includes dementia, encephalopathy, cerebellar degeneration, neuropathies and a syndrome mimicking myasthenia gravis (Lambert–Eaton syndrome).

PRIMARY BRAIN TUMOURS

GLIOMAS

Astrocytoma

This is a low grade tumour derived from astrocytes and occurring most frequently in the cerebrum of young adults.



The tumour which has ill-defined margins grows irregularly into the surrounding brain tissue and only latterly causes increased ICP

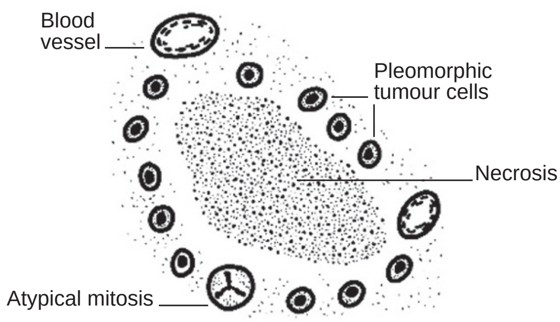
Note enlargement of hemisphere by ill defined growth.

Because they have ill-defined margins, astrocytomas are difficult to eradicate and slowly but inexorably grow and eventually cause death. Many eventually transform to a high grade tumour (anaplastic astrocytoma or glioblastoma). The rare pilocytic astrocytoma occurs in the cerebellum or optic nerve of children and carries a good prognosis.

Glioblastoma

This is the commonest glial tumour and may occur de novo or following a history of low-grade astrocytoma. This is a highly malignant tumour and the cells are pleomorphic, with mitoses, necrosis and a striking proliferation of blood vessels.

The prognosis of these patients is very poor.



Oligodendroglioma

These tumours, derived from oligodendroglia, tend to occur in the cerebrum of adults and may present clinically with epilepsy. They are usually slow growing and often show calcification. Cytogenetic studies have shown that tumours with loss of heterozygosity for 1p and 19p are chemosensitive and therefore have a better prognosis.

Ependymoma

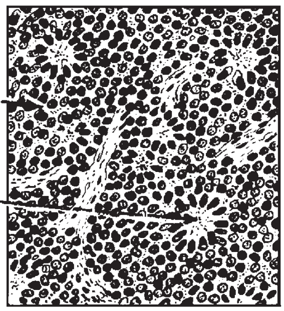
These are also rare and arise from the lining of the ventricles and central spinal cord. They may block the flow of CSF and cause hydrocephalus.

Note: The above gliomas very rarely metastasise outside the nervous system.

TUMOURS OF THE NERVOUS SYSTEM

TUMOURS of NEURONAL TYPE CELLS

Fully differentiated neurones can neither multiply nor give rise to neoplasms. Tumours of this type, derived from primitive nerve precursors (blast cells), are seen in infancy and childhood before completion of differentiation.
They display a basic histological pattern.



Depending on the site of origin, specific names are given:

Cerebellum:
MEDULLOBLASTOMA

Retina:
RETINOBLASTOMA

Sympathetic ganglia (including adrenal medulla):
NEUROBLASTOMA and GANGLIONEUROMA

Medulloblastoma
This highly malignant tumour arises in and spreads over the surface of the cerebellum, often invading the IVth ventricle. Diffuse tumour nodules may develop on surfaces bathed by CSF.

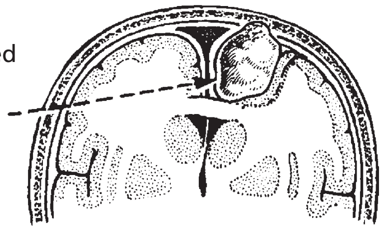
Retinoblastoma
These tumours arise from the retina in children under 3 years. Around 40% of cases are inherited and the tumour may be bilateral. The remaining cases arise sporadically and are usually unilateral. The genetic mechanism involves inactivation of the retinoblastoma gene (RB gene), a tumour suppressor gene situated on the short arm of chromosome 13 (13q14). Untreated the tumour may fill the eye and spread locally into the brain via the optic nerve or systemically after invasion of the choroid. Modern therapy is curative in around 90% of cases. Some inherited cases also develop pinealoblastoma (so-called trilateral retinoblastoma).

Neuroblastoma
These tumours arise from the precursor cells of the autonomic system; the majority occur in the adrenal medulla. They grow rapidly to become large, soft, haemorrhagic and necrotic retroperitoneal masses soon metastasising to lymph nodes, liver and bones.

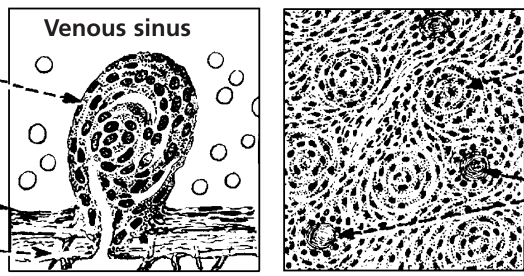
Ganglioneuroma
In some cases, neuronal differentiation proceeds, and mature ganglion cells appear and nerve fibres are formed. In some instances, differentiation is complete; such tumours are found in adult life particularly in the mediastinum where they may grow slowly, eventually causing signs due to their size, but never metastasising. With intermediate degrees of differentiation the name ganglioneuroblastoma is used.

TUMOURS OF THE NERVOUS SYSTEM

Meningiomas
These are thought to arise from arachnoid granulations and so are found most commonly adjacent to venous sinuses. They account for 15–20% of intracranial tumours. They are slow growing and essentially ‘benign’. A few more aggressive tumours may metastasise.



Growth to large size is usually slow so that the compensating mechanisms prevent increased intracranial pressure. Occasional meningiomas arise in the spine.
The histological appearances are variable depending on the relative amounts of cells and collagen, and they mimic in varying degree the arachnoid granulations. Concentric calcified structures (psammoma bodies) are often seen.



Other mesodermal tumours
True vascular neoplasms are rare, but vascular HAMARTOMAS are fairly common and are a cause of intracranial haemorrhage and epilepsy. These lesions show great variation in site, size and complexity.

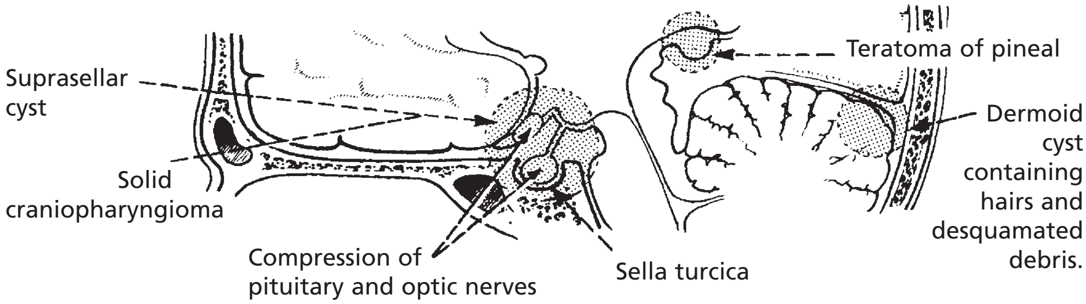
Primary microglial and lymphoid tumours are rare; the latter may be intrinsic to the CNS or be metastatic from a primary tumour outside the CNS. Primary cerebral lymphomas are commonly associated with Epstein-Barr virus and are an important complication of AIDS.

The incidence of CNS lymphomas is apparently increasing. This may be due to better diagnosis and/or to the more common use of therapeutic immunosuppression.

TUMOURS OF THE NERVOUS SYSTEM

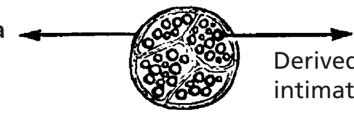
Craniopharyngioma
This is a benign epithelial tumour arising in suprasellar areas. Similar benign cysts also occur.

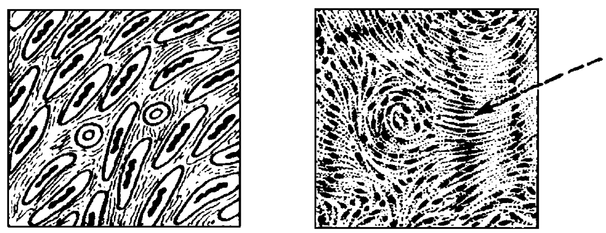
Germ cell tumours
These occasionally arise in midline structures: they are derived from embryologically misplaced germ cells.



TUMOURS OF PERIPHERAL NERVES

These tumours arise in nerve roots within the skull and spine, or in the peripheral nerves. Nomenclature is based on the tissue of origin.





Note: Since neurones do not give rise to these neoplasms, the term neuroma is not used. Traumatic neuroma indicates proliferating nerve endings following injury and is not a true neoplasm (see p.57).

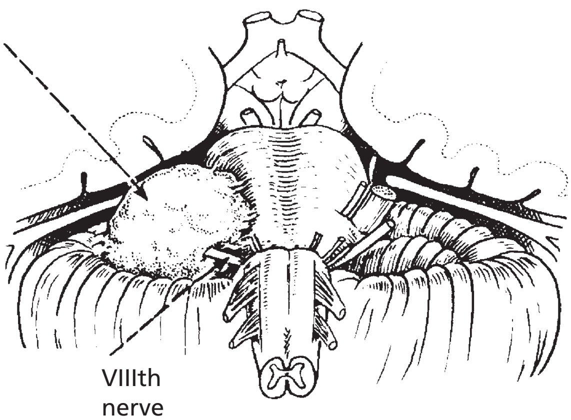
Nerve sheath tumours may be single or multiple; their effects are due to compression of adjacent neural tissue and are seen best within the skull or spinal cord.

TUMOURS OF PERIPHERAL NERVES

SCHWANNOMA

Acoustic Neuroma is a good example. This tumour arises from the VIIIth nerve in the cerebellopontine angle. Although this tumour is benign, it grows around adjacent structures and has an irregular surface so that it may be difficult to remove.

The tumour exerts its effects by compression – distortion of the VIIIth nerve (tinnitus → deafness) and adjacent nerves. Pressure on IVth ventricle → hydrocephalus → increased intracranial pressure.



These tumours are rarely multiple as part of neurofibromatosis Type 2 (associated with NF2 gene on chromosome 22).

Neurofibromas
These may be solitary or, in neurofibromatosis, multiple and affect peripheral nerves over a wide area or occupy a single group of nerves. They form either rounded nodules or fusiform swellings and may be cosmetically disfiguring.

Multiple neurofibromas occur in neurofibromatosis Type 1. This is an autosomal dominant condition caused by a mutation in the NF-1 gene on chromosome 17. Plexiform neurofibroma, which involves a group of nerves forming complex thickening, is considered pathognomonic of neurofibromatosis Type 1.

Unlike schwannomas, a small but significant proportion of neurofibromas undergo transformation to malignant peripheral nerve sheath tumours. The risk is highest when associated with NF-1.

CEREBROSPINAL FLUID

Although the CSF and extracellular fluid of the central nervous system are essentially similar in composition, changes in the CSF are not reliable indicators of disease within the brain parenchyma.

However, since the CSF reflects conditions in the subarachnoid space, in clinical practice detailed examination and analysis are important and are mandatory in suspected meningitis. The important observations using CSF obtained by lumbar puncture are grouped under headings as follows.

NORMAL	**IN DISEASE**			
	Meningitis		**Virus infection**	**Miscellaneous**
	Pyogenic	*Tuberculous*	*Meningo-encephalitis*	
Pressure				
60–180 mmH_2O	↑ Over 200	↑ Over 200	↑High	↓ Below spinal block
Appearance Crystal clear *(for blood staining see below)	Turbid	Opalescent: may be fine fibrin web	Opalescent	–
Cell content 0–4 mononuclears/µl	+++ >1000 Neutrophils	+++ Lymphocytes	± + Lymphocytes	–
Biochemistry Protein 0.2–0.4 g/l	↑ 1–10 g/l	↑ 1–3 g/l	↑ 0.5–2 g/l	Very high in spinal block
Glucose 50–80 mg/100 ml (2.8-4.4 mmol/l)	greatly↓ or absent	Low 20–30 mg	Normal	Normal

* When the CSF is blood-stained, it is important to distinguish between contamination due to trauma caused by the tap and true intracranial haemorrhage.

	Contamination	**True haemorrhage**
Supernatant after centrifugation	Clear	Yellow due to bilirubin (red cell degeneration)
Cell count – leucocyte:RBC ratio	Normal	Increased

Microbiology. Identification of organisms is very important.

(1) Deposit and/or fibrin web – stained
- Gram – pyogenic bacteria and fungi
- ZN – tubercle bacilli

(2) Culture: virus isolation

(3) Tests for microbial antigens
- VDRL for syphilis
- Immunoelectrophoresis for other antigens

THE EYE

CATARACT

The normal lens consists of soluble crystalline proteins encased within elongated lens fibre cells surrounded by an elastic lens capsule. There is also a layer of lens epithelium beneath the anterior capsule. The metabolism of the lens depends on diffusion of nutrients from the aqueous. In cataract the lens is opaque either because of disorganisation of the fibre membranes at a microscopic level or of the lens proteins at a molecular level. Cataract is one of the most common and treatable causes of blindness worldwide.

Aetiology of Cataracts

Developmental: due to congenital malformation or toxic damage to lens fibres, e.g. Rubella.

Trauma: In blunt trauma, resulting shock waves may rupture lens fibres. In penetrating trauma, rupture of the lens capsule leads to fibre disruption and alterations in fluid content.

Inflammation: inflammatory mediators alter the constituents of the aqueous.

Metabolic Disease: hypocalcaemia and diabetes alter the consituents of the aqueous.

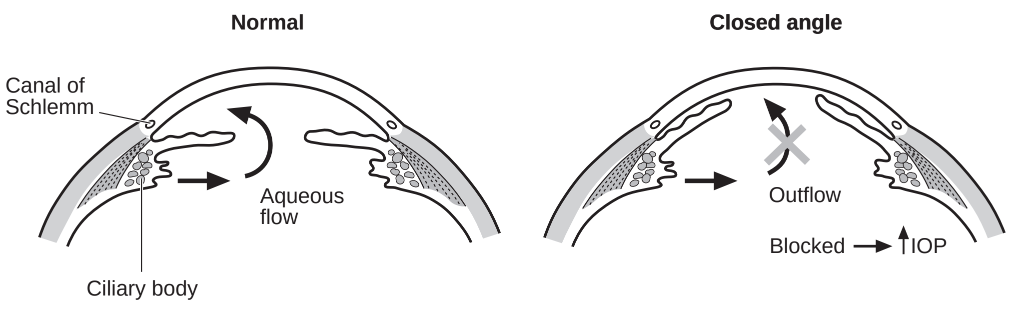
Senile: due to degradation of lens proteins in the oldest central part of the lens.

GLAUCOMA

This is a common cause of blindness in the Western World. Glaucoma occurs when intraocular pressure (IOP) rises to an extent which causes damage to tissues within the eye.

Normal

IOP is maintained by a balance between aqueous production by the ciliary body and outflow via the trabecular meshwork (TM) and canal of Schlemm.



Types

Open angle

(a) Primary – acquired disease due to increased resistance in the TM.
(b) Secondary – due to blockage of the TM by tumour cells, leaked lens protein, etc.

Closed angle

(a) Primary – the iris root becomes opposed to the TM. This is in part due to anatomical variations in the anterior segment. It is, for example, more common in East Asian and Inuit groups with a shallower anterior chamber.
(b) Secondary – due to intraocular neovascularisation, e.g. diabetes, ocular ischaemia

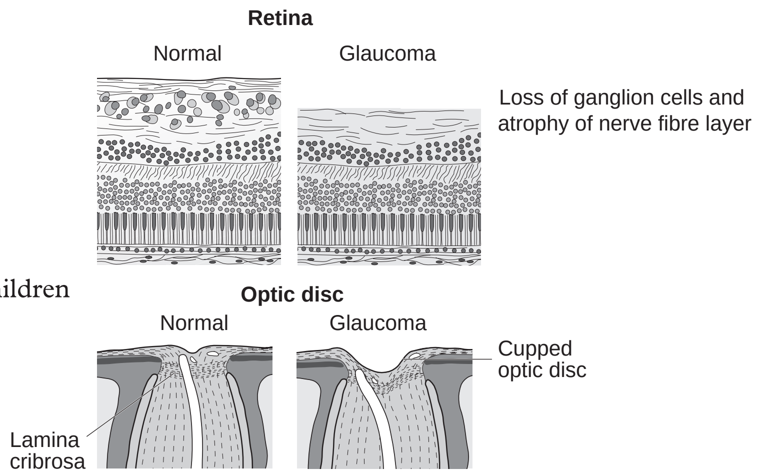
Congenital – due to malformation of the TM.

THE EYE

GLAUCOMA *(continued)*

Effects of increased IOP

Corneal oedema
Iris ischaemia
Ciliary body atrophy
Cataract
Retinal atrophy
Cupping of optic disc
Enlargement of the eye in children (buphthalmos = ox eye)



TUMOURS

Retinoblastoma is the most common primary intraocular tumour of childhood. This is discussed on page 577.

Melanoma

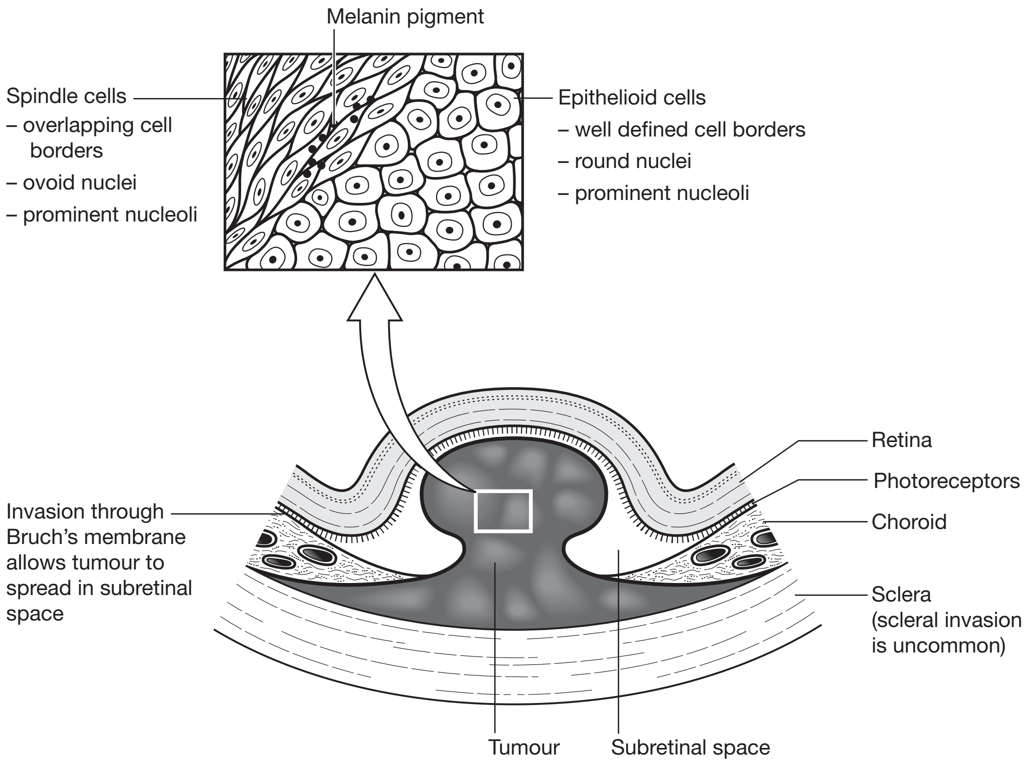
This is the most common primary intraocular tumour in adults. It can occur anywhere in the uveal tract. Iris melanomas usually present early, as they are visible. Ciliary body melanomas present late with visual disturbances or glaucoma due to invasion of the trabecular meshwork. Choroid melanomas may be asymptomatic and picked up at routine eye checks or later present with symptoms secondary to associated retinal detachment.

Pathology

Mushroom shaped tumour due to spread beneath retina.
Spindle cells (better prognosis).
Epithelioid cells (poorer prognosis)
(The majority of tumours are mixed.)
Cytogenetics-loss of one copy of chromosome 3 (Monosomy 3) carries a poor prognosis.

THE EYE

TUMOURS *(continued)*



Secondary Tumours

Metastasis is the commonest type of intraocular malignancy. These usually occur in the choroid and the most common primary sites are breast and lung.

CHAPTER 15

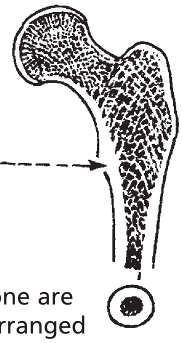
MUSCULO-SKELETAL SYSTEM

BONE

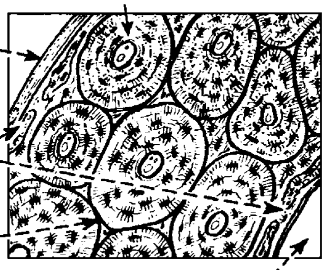
There are two different forms of normal adult bone, both with a lamellar (layered) structure.

1. **COMPACT BONE**

seen in long bone shafts and forms the dense outer shell (cortex).

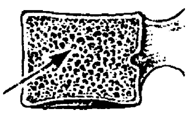


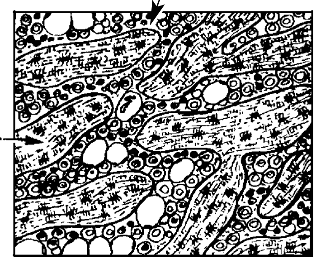
The basic units of compact bone are Haversian systems (osteons) arranged in vertical columns.



2. **CANCELLOUS BONE**

found within medullary cavities along with bone marrow. The major form in vertebral and in flat bones such as the pelvis.





The basic unit of cancellous bone is the trabecula, arranged along lines of stress.

Note: Cancellous bone comprises 20% of bone mass but 80% of bone turnover due to its large surface area

WOVEN BONE (non-lamellar), is a primitive form laid down in fetal development. In adult life, this type is seen in bone repair and bone-forming tumours. It can be remodelled to be replaced by lamellar bone.

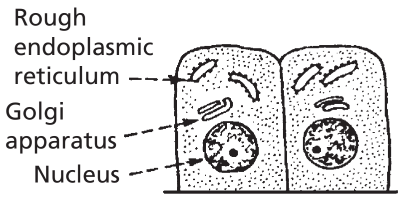


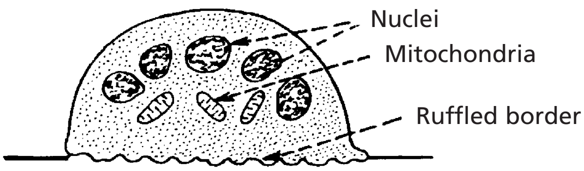
Bone and calcium

Bone acts as a reservoir for calcium, which is maintained within a narrow range (2.1–2.6 mmol/l). Hypocalcaemia stimulates parathyroids to produce parathyroid hormone (PTH) which promotes bone resorption, calcium absorption from the gut and reabsorption from the kidney. As the serum calcium rises, PTH production is switched off.

BONE TURNOVER

Bone is formed by osteoblasts and removed by osteoclasts.





OSTEOBLASTS

– derived from osteoprogenitor cells.
– produce Type I collagen and other proteins.
– secrete alkaline phosphatase – a marker of bone formation.
– stimulated by mechanical stress, androgens, cytokines, e.g. TGF-β

OSTEOCLASTS

– derived from marrow precursors.
– produce acid and enzymes to remove bone.
– produce collagen degradation products e.g. urinary HO proline – a marker of bone destruction.
– stimulated by cytokines e.g. IL-1, IL-6 (indirectly by PTH).
– inhibited by oestrogens.

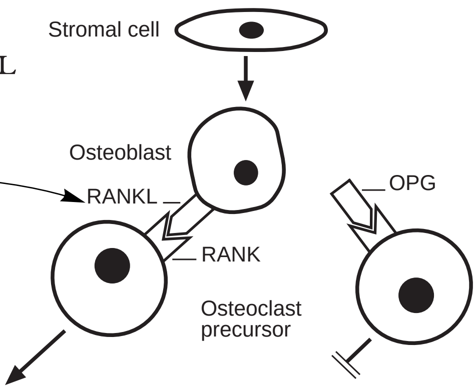
The activities of the two cell types are closely 'coupled' in the normal process of bone turnover. In the adult 10% of the skeleton is replaced annually. The process has *activating* and *inhibitory* arms.

ACTIVATION

Osteoblasts bear RANKL (**R**eceptor **A**ctivator of **N**F-κB **L**igand)

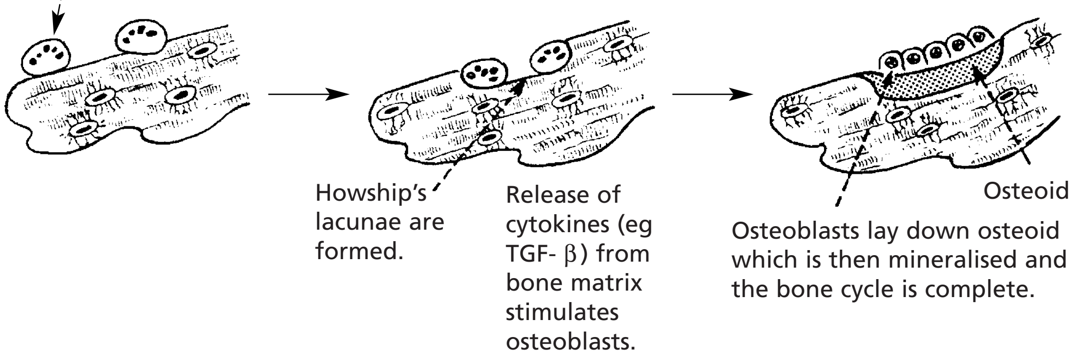
Binds to RANK

Proliferation and differentiation into osteoclasts



INHIBITION

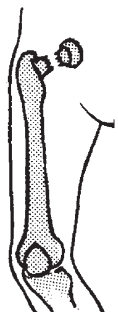
Under other circumstances osteoblasts and other cells produce osteoprotegerin (OPG) a soluble molecule which blocks activation through RANK.



OSTEOPOROSIS

OSTEOPOROSIS is the commonest disorder of bone.
It is defined as a systemic disease characterised by:

(1) low bone mass.
(2) microarchitectural deterioration of bone, with
(3) an increase in bone fragility and susceptibility to fracture.



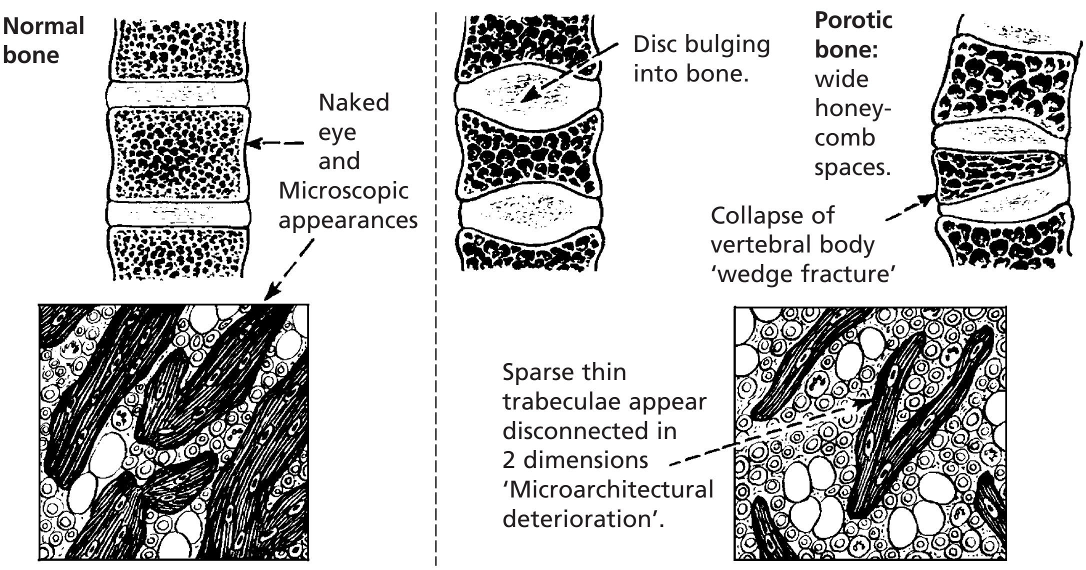
A patient is said to have osteoporosis if BONE MINERAL DENSITY >2.5 standard deviations below the mean of normal young subjects.

Clinical effects: – osteoporosis is a disease predominantly of post-menopausal females, but men are also affected.

1. It causes bone fractures (collapse) of vertebral bodies with loss of height and kyphosis.
2. Fracture of neck of femur or other long bones (especially Colles' fracture of distal radius).

Note: In osteoporosis, the routine serum biochemical tests – particularly the calcium levels – are within the normal range.

Pathology: The changes in the vertebral bodies are shown.

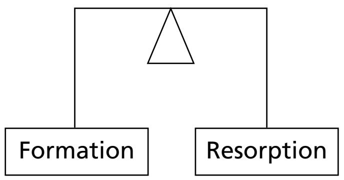


Note: (i) The bone has a normal calcium content.
(ii) Bone loss is most marked in cancellous bone with its high turnover, but cortical bone is also affected.

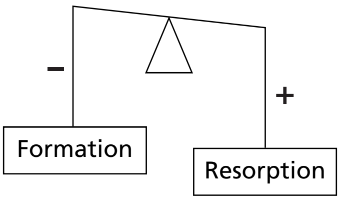
OSTEOPOROSIS

Aetiology

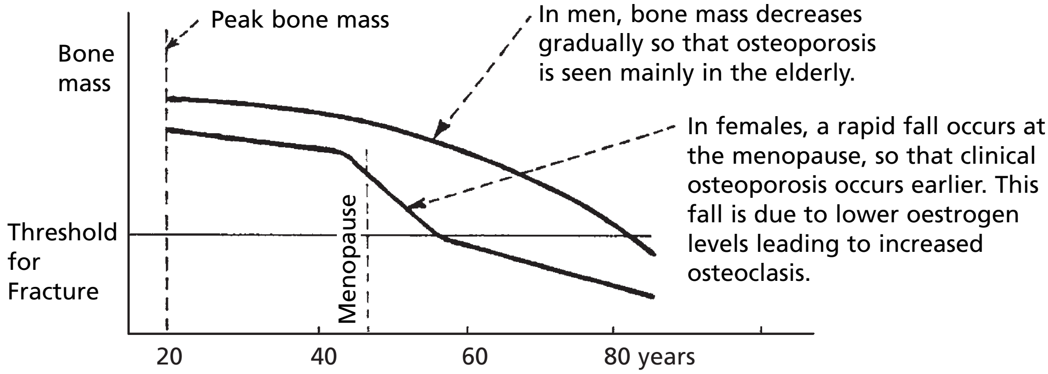
In *normal* bone the dynamic processes of formation and resorption are in balance.



In *osteoporosis* the balance is upset by
(1) diminished formation
(2) increased resorption, or both



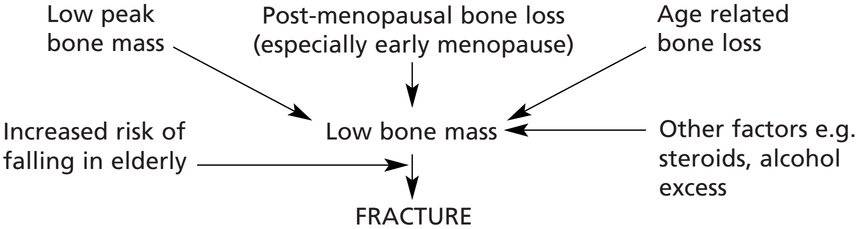
Bone mass decreases with age in both sexes: in old age, osteoblastic activity falls.



PEAK BONE MASS is important – a high initial figure makes osteoporosis less likely. This depends on factors including:

(a) Genetic predisposition – polymorphisms of Type I collagen gene and other genes regulating bone cell activity.
(b) Nutrition – especially calcium intake.
(c) Exercise.

The **aetiology** can be summarised as follows:



Localised osteoporosis is commonly due to disuse and is seen as a complication of other disorders, e.g. local IMMOBILISATION following fracture; limb paralysis and adjacent to severe joint disease with limitation of movement.

OSTEOMALACIA AND RICKETS

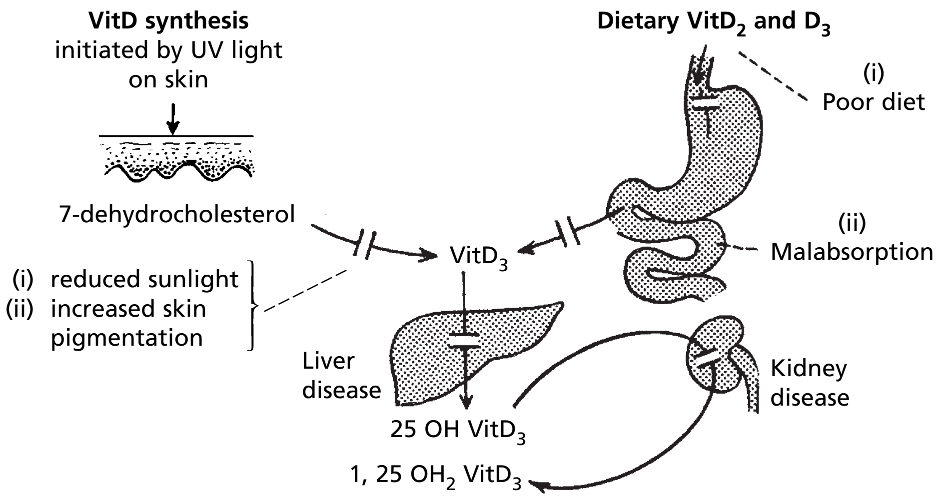
Osteomalacia and rickets are disorders of bone due to failure of mineralisation of newly formed osteoid, caused by vitamin D deficiency in almost all cases. The poorly calcified bones are soft causing deformity or fracture.

Osteomalacia occurs in adult life and affects the osteoid which is being continually laid down in the normal remodelling of bone.

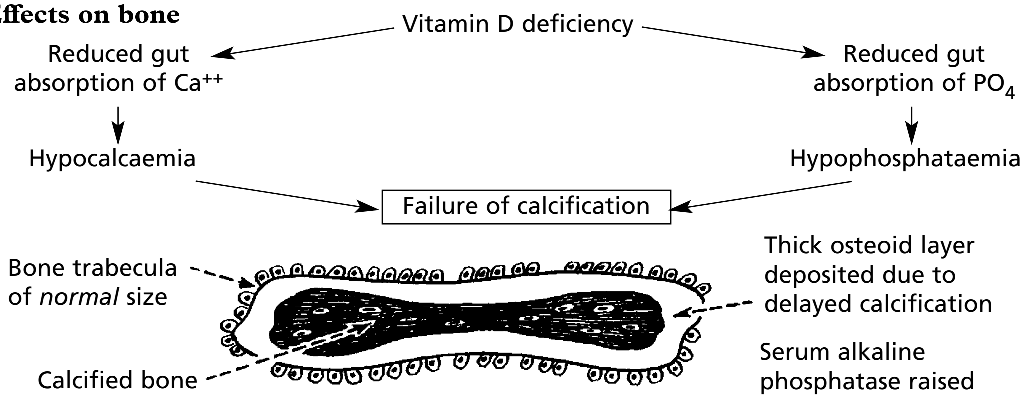
Rickets affects the growing child. As well as deformity and fractures, there is disturbance of growth plates. X-ray may show linear partial fractures of long bones which have failed to calcify (Looser's zones).

The following simplified diagrams indicate the causes of vitamin D deficiency and its effects on bone.

Causes of deficiency:



Effects on bone

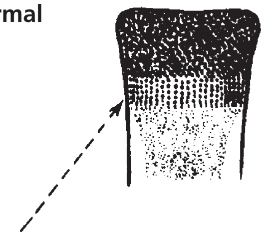


Note: The hypocalcaemia seen in osteomalacia stimulates an increase in PTH levels and mild hyperparathyroidism.

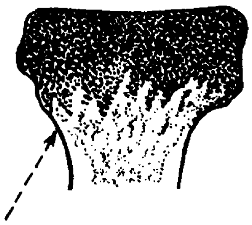
METABOLIC BONE DISEASE

In **rickets** the growing ends of long bones are abnormal.

Normal



Rickets



This results in stunting of growth and bowing of the lower limbs.
In females permanent deformities of the pelvis can cause serious difficulty during childbirth.
Enlargement of costo-chondral junctions gives the so-called rickety rosary

HYPERPARATHYROIDISM (see p.642)

Bone changes may be seen in hyperparathyroidism, especially when severe or long-standing. There is increased bone resorption due to PTH-induced osteoclastic activity. Due to 'coupling', osteoblastic activity is also increased but the net effect is bone loss.



These changes affect all bones. There may be marked loss of bone with numerous osteoclasts and haemosidern pigment – the so-called 'brown tumour of hyperparathyroidism', which can mimic giant cell tumour.

RENAL OSTEODYSTROPHY

Bone disease is common in chronic renal failure. It is a combination of osteomalacia and hyperparathyroidism, together with loss of bone synthesis.

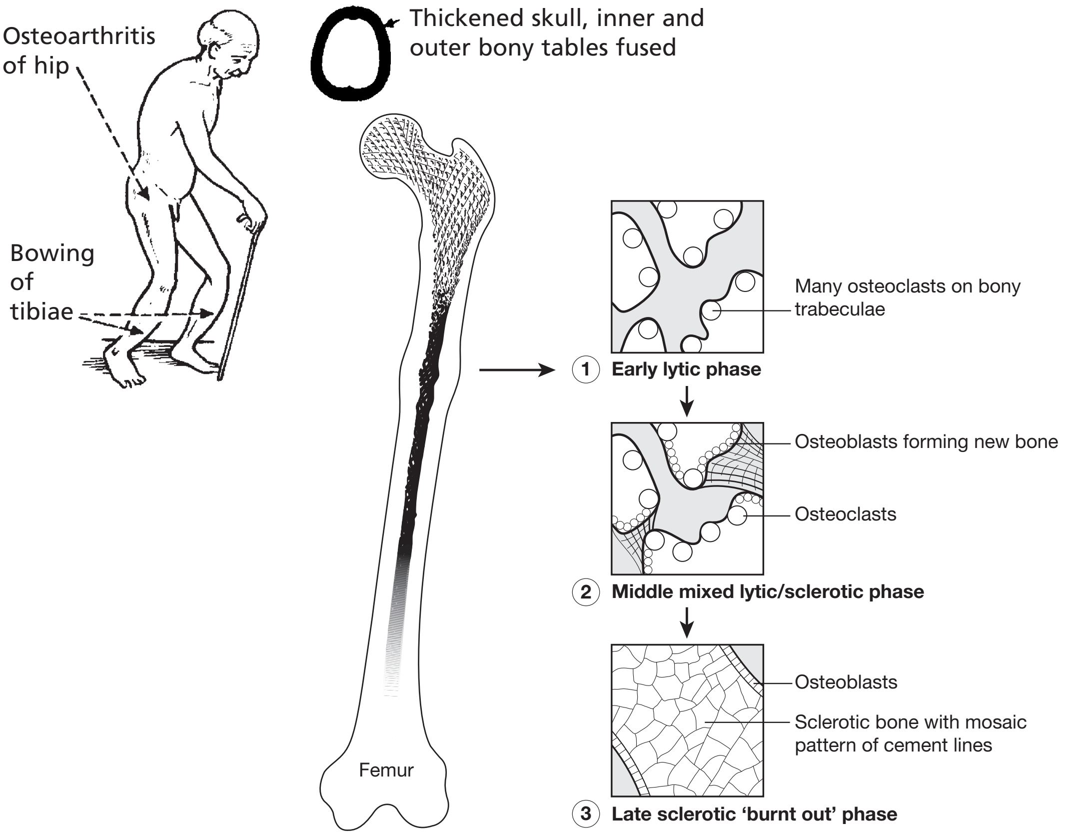
Reduced 1,25 D_3 → **OSTEOMALACIA** → RENAL OSTEODYSTROPHY

Decreased plasma CALCIUM → **'SECONDARY' HYPERPARATHYROIDISM** ↓ Increased OSTEOCLASIS → RENAL OSTEODYSTROPHY

Reduced bone formation → 'ADYNAMIC BONE DISEASE' → RENAL OSTEODYSTROPHY

PAGET'S DISEASE OF BONE

This disease of unknown aetiology usually presents after the age of 50 years and is more common in males. It is fairly common (3% of autopsies), but only in its more severe forms are there clinical symptoms. The disorder is focal: the bones particularly affected are the pelvis, vertebrae, skull and lower limbs. It has been suggested that virus infection (e.g. measles, distemper) of osteoclasts is responsible. Genetic factors are important.



To begin with, there is a localised increase in **osteoclastic** activity causing bone resorption; soon there is a marked **osteoblastic** reaction with bone resorption and deposition proceeding chaotically, so that irregular bone trabeculae with mosaic cement lines are formed. The bone may be thickened, but its structure is defective and weak. Biochemical changes reflect the cellular activity at trabecular level: *Alkaline phosphatase* ↑(osteoblastic); *urinary hydroxyproline* ↑(collagen destruction).

Often asymptomatic, the main effects are:

- Bone pain and deformity
- Pathological fracture
- Osteoarthritis (due to abnormal stresses caused by bone deformity)
- Nerve compression leading to deafness or spinal cord compression
- An increased risk (×30) of the development of bone sarcoma.

The use of bisphosphonates offers effective therapy in many cases.

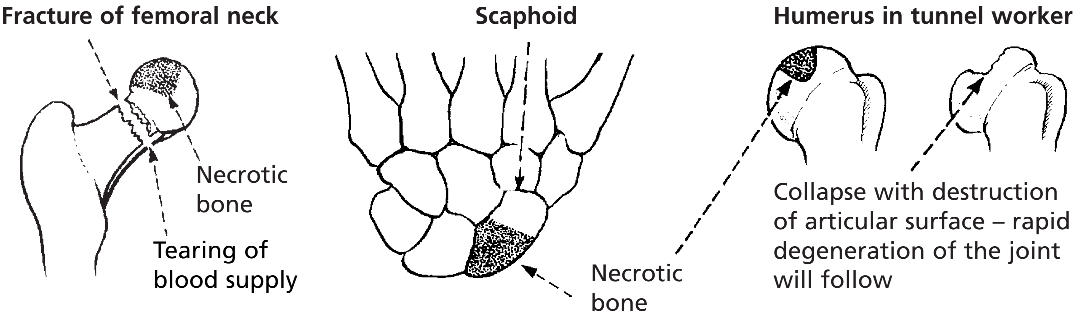
BONE – MISCELLANEOUS

OSTEONECROSIS (AVASCULAR NECROSIS)

Interruption of its blood supply causes bone to undergo necrosis. This tends to occur with fractures at sites where the vascular supply is damaged. Fractures of the femoral neck and scaphoid bone are good examples.

Non traumatic causes include corticosteroid therapy, alcoholism, sickle cell anaemia, Gaucher's disease and historically in decompression in those working in increased atmospheric pressure (caisson disease).

Bone necrosis occuring at an articular surface often leads to degenerative arthritis.

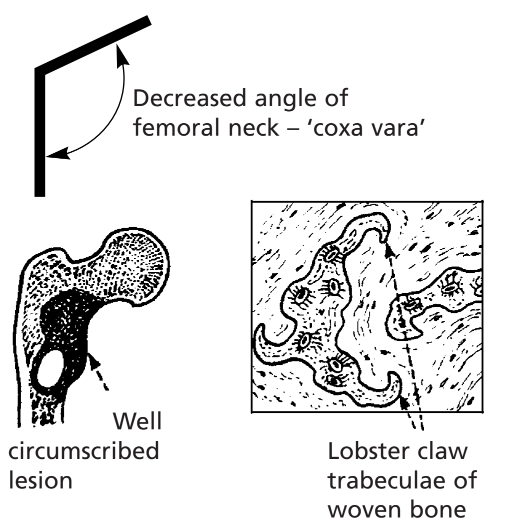


Note: These areas of necrotic bone may appear radiodense due to disuse osteoporosis of the adjacent living bone.

In children and adolescents osteonecrosis occurs at several epiphyseal sites probably due to trauma). The commonest is Perthes' disease in which necrosis of one or both femoral heads occurs in children aged 4–10 years (male: female = 5:1).

FIBROUS DYSPLASIA OF BONE

This disorder may affect one (monostotic) or several (polyostotic) bones. On histology, well demarcated fibrous tissue containing small abnormal woven bone trabeculae is seen. Somatic mutations of the GNAS1 gene which encodes the α subunit of a stimulatory G-protein are responsible. Whether the disease is polyostotic or monostotic depends on the stage of development of the embryo when the mutation occurs, a state known as mosaicism.



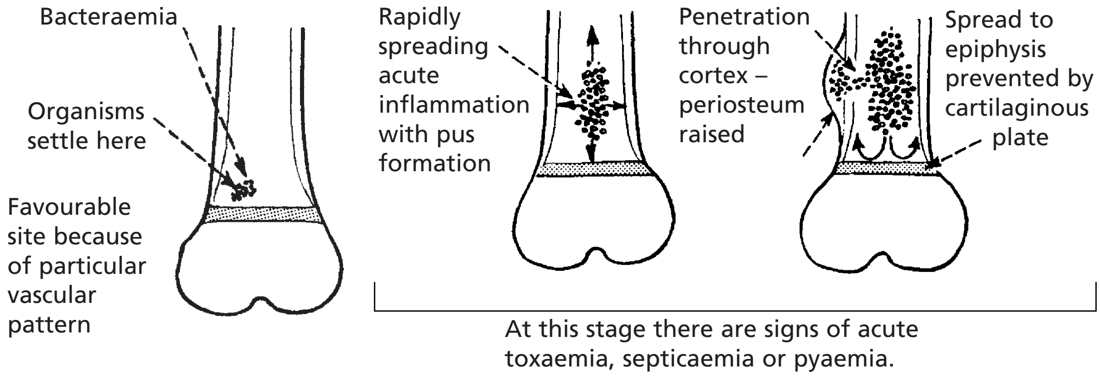
Complications

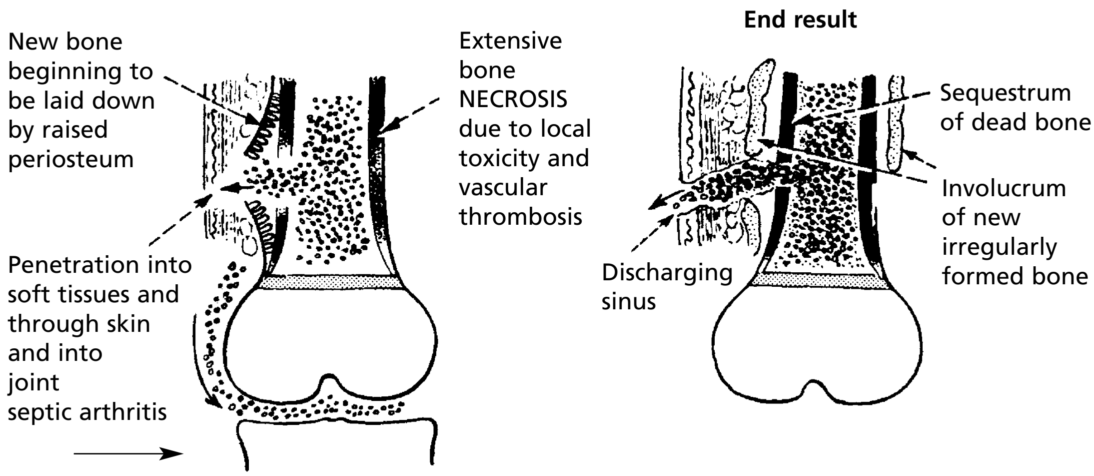
Fracture or deformity of the weakened bone.

INFECTIONS OF BONE

ACUTE OSTEOMYELITIS

Classically caused by *Staphylococcus aureus*. This affects the metaphyses of long bones in children. Nowadays the incidence has been greatly reduced and the use of antibiotics aborts the development of the disease. The bacteria are blood borne and settle in the cancellous bone of the metaphysis. The effects are dramatic and rapidly progressive.





The presence of necrotic bone ensures that the inflammation continues.

The late complications are chronic osteomyelitis, disturbance of bone growth, AMYLOID disease may occur and occasionally squamous carcinoma arises in a sinus.

Other pyogenic bacteria can cause osteitis – the salmonella group (esp. *S. typhi*) and brucella, the latter often causing a low grade osteitis of the spine.

With inadequate antibiotic treatment, acute inflammatory processes may be converted into low grade osteitis. Staphylococcal infection of the spine may present in adults in this way.

INFECTIONS OF BONE

TUBERCULOSIS

The incidence of bone and joint infection parallels that of the more common pulmonary infection. It is therefore low in developed countries but still significant elsewhere, and has risen in association with HIV infection.

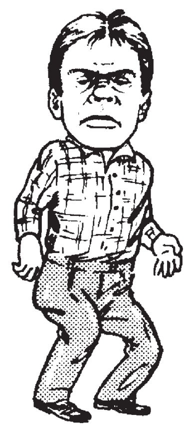
The spine and growing ends of long bones including the epiphyses are affected by blood borne spread and the infection spreads to the adjacent joints.

Bone is destroyed and replaced by granulomatous inflammation with caseous necrosis. Spinal infection spreads into adjacent tissues and leads to 'cold abscess' formation.

Although the progress is much less rapid than in acute osteomyelitis, without adequate treatment serious damage to bones and joints occurs.

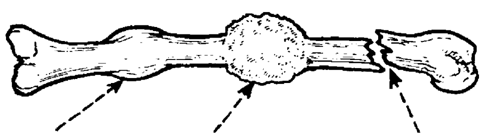
DEVELOPMENTAL ABNORMALITIES

Generalised abnormalities are rare and usually inherited.



1. **ACHONDROPLASIA** is the commonest cause of dwarfism, with short, deformed limbs and a waddling gait. The bones at the skull base are underdeveloped.
   A mutation of the fibroblast growth factor receptor gene (FGFR3) is responsible, which causes constitutive activation and inhibits cartilage growth. Although inherited as an autosomal dominant trait, 80% of cases result from new mutations.
2. In **OSTEOGENESIS IMPERFECTA** (Brittle bone disease) the thin brittle bones fracture easily and a history of multiple fractures with minimal cause is the usual presentation. It is important to distinguish this from 'non-accidental injury'.
   The basic defect is in the osteoblasts which fail to synthesise collagen properly, due to mutations affecting the Type I collagen genes on chromosomes 7 and 17. The severity of the disorder depends on the type of mutation, some cases being lethal in utero.

A long bone showing three fractures.



Patients may have:
(a) very thin sclerae which appear blue
(b) abnormal tooth development due to defective dentine formation.

DEVELOPMENTAL ABNORMALITIES

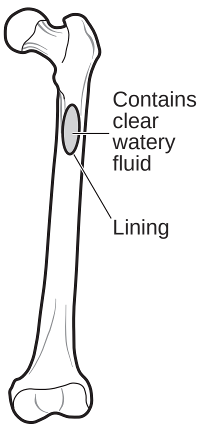
3. **OSTEOPETROSIS** (Marble bone disease of Albers–Schönberg) is a disorder in which osteoclasts are absent or defective. This results in failure of bone remodelling and abnormal conversion of cartilage to bone. The whole skeleton becomes dense and the bones thickened, but weakened.

   Complications are: (a) anaemia due to failure of development of the bone marrow cavity
   (b) fractures
   (c) cranial nerve compression.

   Bone marrow transplantation provides functioning osteoclasts and reverses the skeletal abnormalities.

CYSTS OF BONE

Simple bone cysts (unicameral-single chamber) have a thin fibrous lining and occur in the proximal humeral and femoral metaphyses of children. They often present with fracture.



Aneurysmal bone cysts (expanding blood-filled cysts in adolescents) are eccentric expanding blood-filled cysts presenting with swelling, pain or fracture.

These true cysts should not be confused with lytic lesions which appear cystic on X-ray.

TUMOURS IN BONE

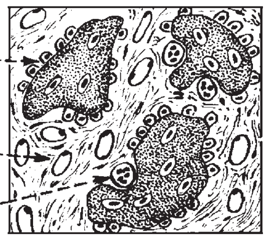
Primary bone tumours are rare. There are both benign and malignant forms, examples of which follow. In contrast, metastatic tumours and myeloma are common.

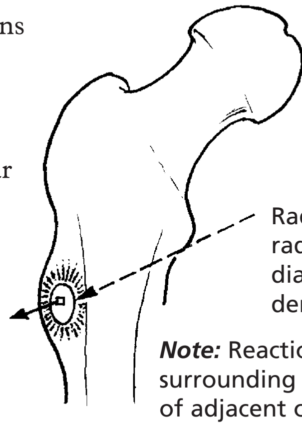
OSTEOID OSTEOMA

This uncommon benign tumour has a striking clinical presentation and a distinctive pathology.

Clinical: Classically, an adolescent complains of well localised, increasingly severe bone pain. Aspirin and non steroidals give relief.

Pathological: The essential lesion is a small focus (nidus) of newly formed irregular trabeculae of osteoid or poorly calcified woven bone in a highly vascular stroma.

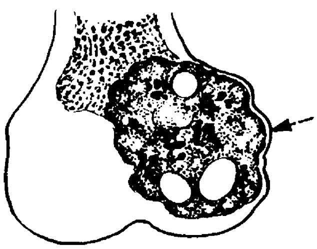


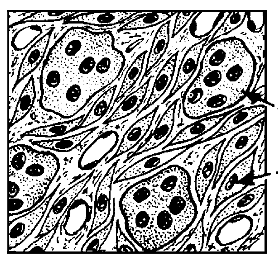


GIANT CELL TUMOUR (osteoclastoma)

This uncommon tumour presents in adult life (age 20–40 years), at the end of a long bone, especially adjacent to the knee. The tumour destroys bone and the cortex gradually expands, becoming egg-shell thin. Pathological fracture is common.

The histology is characteristic:

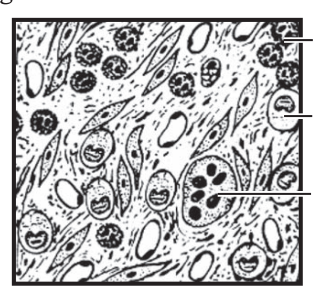




Behaviour: Almost all giant cell tumours are benign. Most are cured by thorough removal: approximately 20% recur: well under 5% become malignant and metastasise to the lungs.

EOSINOPHILIC GRANULOMA (at the benign end of the spectrum of Langerhans histiocytosis) usually presents as single osteolytic radiolucent lesions of bone in children. Vertebral collapse and pathological fractures are sometimes seen.

The prognosis is usually good.
The histological appearances are typical.



TUMOURS IN BONE

MALIGNANT TUMOURS

Primary malignant tumours of bone are not common, but they are important as many arise in young people and are highly malignant. Some arise in older people with pre-existing bone disorders, e.g. Paget's disease, previous irradiation.

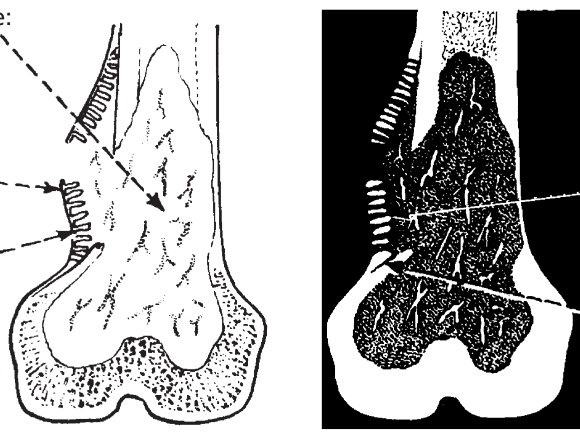
Osteosarcoma

This highly malignant tumour is the commonest primary malignant tumour of bone. It affects two distinct age groups and there is a preponderance of males over females.

Young age group – majority of cases (10–25 years)
The tumour usually arises near the end of a limb long bone (particularly around the knee).

Elderly subjects (over 60 yrs.)
In 50% of this group, Paget's disease is associated. Long bones, vertebrae and pelvis are often affected, and tumours may be multicentric in origin.

The 'classic' tumour in an adolescent begins in the metaphysis of the medullary cavity. Most patients complain of bone pain and when the tumour penetrates the cortex there may be a soft-tissue swelling.



Note: At this stage lung metastases may be present.

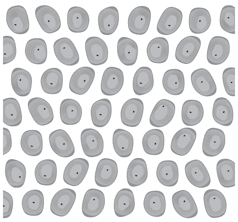
Histologically, varying amounts of osteoid, woven bone and sometimes islands of primitive cartilage are seen. The tumour cells are pleomorphic and mitotically active. With modern chemotherapy 50–60% of patients survive for 5 years.

TUMOURS IN BONE

Chondrosarcoma
This shows a much slower growth pattern and affects the age group 40–70 years. Multiple enchondromatosis pre-exists in a small number of cases. The tumours arise particularly in the limb girdles and proximal long bones and consist of lobules of cartilage. Progressive local extension is usual. Metastases, usually to the lung, are rare.

Ewing's sarcoma
This rare malignant tumour affects the young (age 5–20 years) and arises in long bones, pelvis, ribs and scapulae. It is very aggressive, metastasising early to lungs and other bones.

The tumour cells are small and uniform. Fever and an elevated white count are common and may mimic osteomyelitis. The histological appearances may mimic lymphoma.



Ewing's sarcoma is a primitive neuro-ectodermal tumour associated with translocation and fusion of genes, typically the *EWS* and *Fli-1* genes, on chromosomes 11 and 22. With chemotherapy, survival is similar to that of osteosarcoma.

Lymphoid tumours
Lymphoma and myeloma (see p.435) may arise in bone, causing bone destruction.

SECONDARY TUMOURS IN BONE

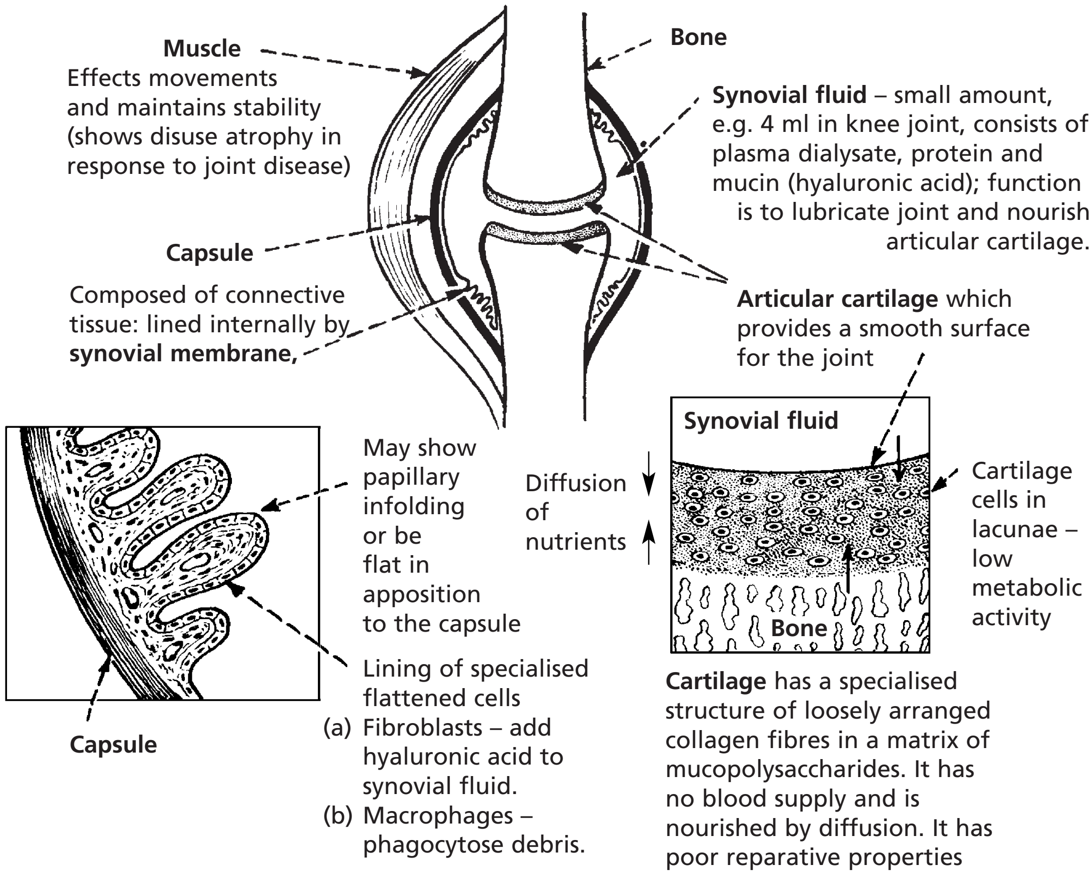
THIS IS BY FAR THE MOST COMMON TYPE OF TUMOUR IN BONE.

Tumours which show a predilection for spread to bone are carcinoma of the PROSTATE, BREAST, LUNG, KIDNEY and THYROID. Metastases are usually multiple. The incidence of bone secondaries ESPECIALLY IN THE SPINE is very high when these tumours become widespread. Occasionally latent renal and thyroid cancers present as a single bony metastasis with pathological fracture.

Metastases are usually osteolytic with extensive destruction of bone. In a minority of cases, osteoblastic activity is stimulated by the presence of the tumour so that dense reactive bone is formed. Osteosclerotic secondaries of this type are seen particularly in cancers of the PROSTATE and BREAST.

JOINT DISEASES

The diagram illustrates the structure of a **synovial joint.**



Cartilage has a specialised structure of loosely arranged collagen fibres in a matrix of mucopolysaccharides. It has no blood supply and is nourished by diffusion. It has poor reparative properties and tends to be replaced by fibrous tissue.

The two most common joint diseases illustrate how individual components of a joint may be initially affected:

Rheumatoid Arthritis essentially an inflammation of **synovial membrane**	**Osteoarthritis** essentially a degeneration of **articular cartilage**

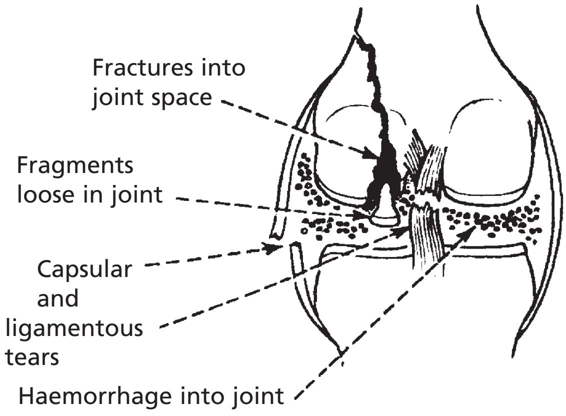
As the diseases progress, other secondary effects are added and may obscure the basic pathology.

JOINT TRAUMA

Trauma is very variable in its severity and effects.
At one end of the scale a single incident of 'sprain' or 'strain' involves only minor soft tissue damage with minimal associated haemorrhage – in these circumstances the healing capacity of joints is rapid and complete.

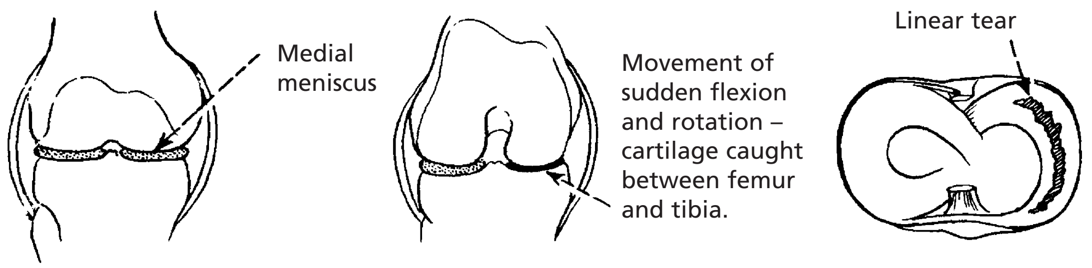
With mild degrees of trauma, particularly if repeated, the synovial membrane shows non-specific reactive changes which include hyperaemia and a mild chronic inflammatory cellular infiltrate. There is often a joint **effusion**.

Serious damage to joints include:



Possible sequels are:
1. The articular surface is permanently deformed (ineffective repair of cartilage).
2. Loose body continues to cause traumatic damage to cartilage.
3. Ligaments may not heal or are united by poor scar tissue.

The medial meniscus of the knee is susceptible to tears:



Locking of the joint and effusion are common.

Apart from damage directly attributable to trauma, the most important consequence is an increased risk of osteoarthritis.

OSTEOARTHRITIS (OA)

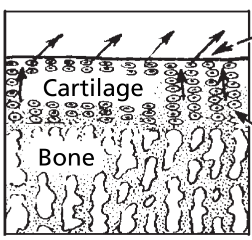
OSTEOARTHRITIS (OA)

This is the commonest disorder of joints and, by causing pain and stiffness, is the commonest cause of chronic disability after middle age. The basic pathology is degenerative and is similar to the changes of ageing.

The disorder is divided into two main groups. In both types of osteoarthritis the basic pathological processes are the same.

1. In **secondary OA** there is a clear association with some predisposing condition which may be virtually any abnormality of a joint. Of particular importance are:
   a) abnormality of the articular surfaces (e.g. following injury).
   b) abnormal stresses on the joint (e.g. the increased weight-bearing demanded by obesity; association with particular occupations and sports), or abnormal alignments.
   c) previous inflammation e.g. rheumatoid arthritis, sepsis.
2. In **primary OA**, no obvious predisposing cause is evident, but often runs in families. In some, mutation of Type II collagen gene is found.

Normal



Surface loss

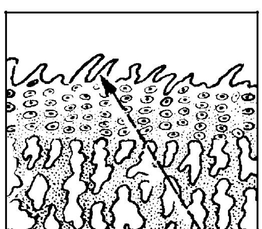
Replacement by chondrocytes

The integrity of the articular cartilage represents a balance between 'wear and tear' losses and replacement by chondrocytes of the specialised matrix.

The earliest change in ageing and OA is in the chemical composition of the matrix which becomes softer. This is followed by progressive characteristic morphological changes.

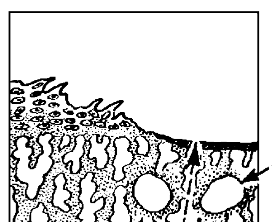
At site of weight bearing

Early OA



Flaking and fibrillation of surface

Later OA

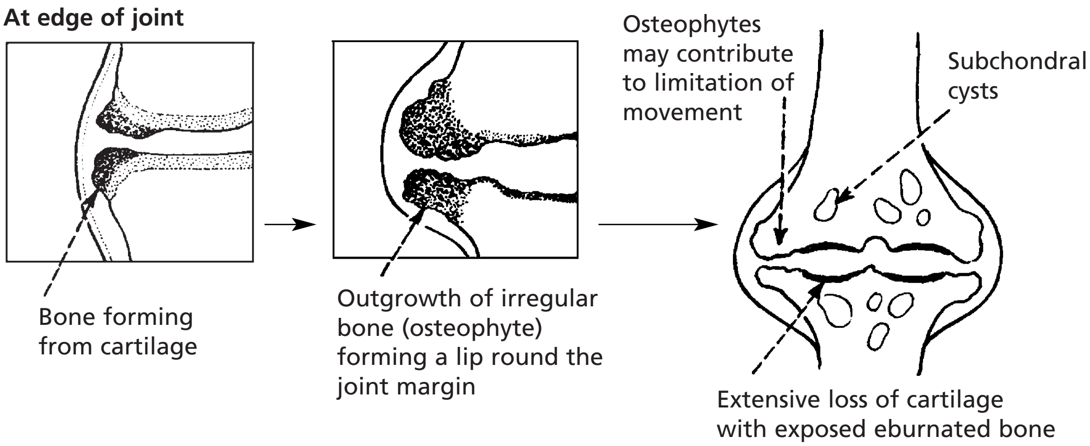


Areas of cystic degeneration

Loss of cartilage; exposure of bone which becomes hard and polished (eburnated)

OSTEOARTHRITIS (OA)

OSTEOARTHRITIS (*continued*)



The synovial membrane may show mild, non-specific inflammation and effusion may occur but these changes are secondary.

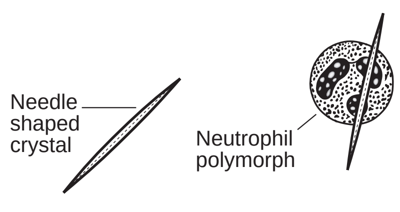
Distribution: secondary OA often affects a single predisposed joint.

In primary OA, the larger weight bearing joints and the spine in particular are susceptible, but interphalangeal joints bear osteophytic outgrowths (Heberden's and Bouchard's nodes). Osteoarthritis is the main indication for hip and knee replacement surgery.

A particularly severe form (Charcot's joint) is seen when the nerve supply to a joint is defective – neuropathic arthropathy.

GOUT

Patients with gout develop acute arthritis often of the great toe. Uric acid is produced in purine (DNA) breakdown. In gout, there is hyperuricaemia (serum uric acid >7 mg/dl). Periodically, urate crystals are deposited within the affected joint, at first in the articular cartilage, but chronically in the adjacent bone and soft tissues forming masses known as tophi. Joint aspiration shows characteristic appearances.



PSEUDO-GOUT. In this condition of the elderly, rhomboid crystals of calcium pyrophosphate are deposited in the joint, evoking a similar inflammatory reaction. Larger joints such as the knee tend to be affected; chronic degenerative arthritis often supervenes or co-exists. The radiological appearances are known as chondrocalcinosis.

RHEUMATOID ARTHRITIS (RA)

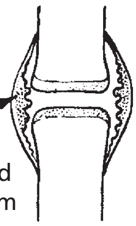
Rheumatoid arthritis (RA) is a common systemic disease (1–3% of population in Europe). The most affected tissue is the synovial membrane. The typical clinical course is insidious in its onset and progression; in a minority, the onset is acute and the progress rapid. Frequently there are remissions and exacerbations.

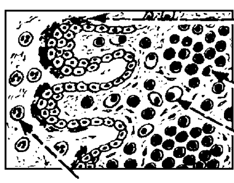
Incidence: female > male 3:1 *Age of onset:* usually 35–55 years, but also in childhood – usually severe.

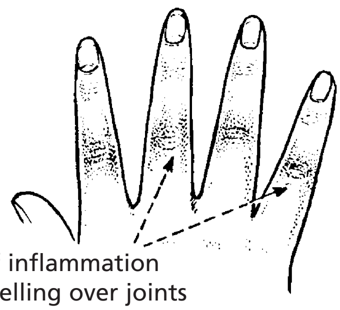
Typically, affecting multiple joints symmetrically, the joints of the hands and feet and the knee joints are affected; there may be involvement of the spine.

Pathology: The synovial membrane shows chronic inflammation.

Early

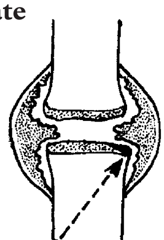


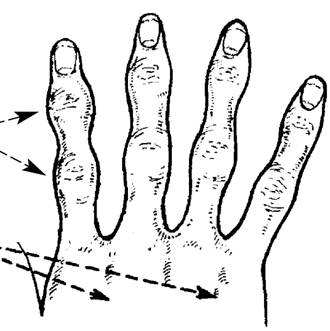




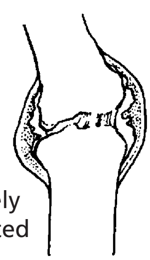
A raised ESR and normochromic anaemia are evidence of the systemic illness.

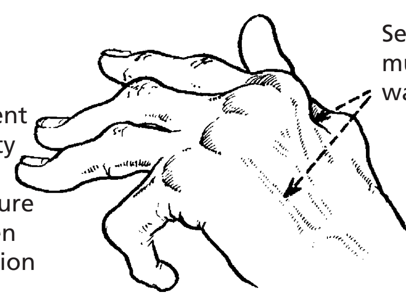
Intermediate





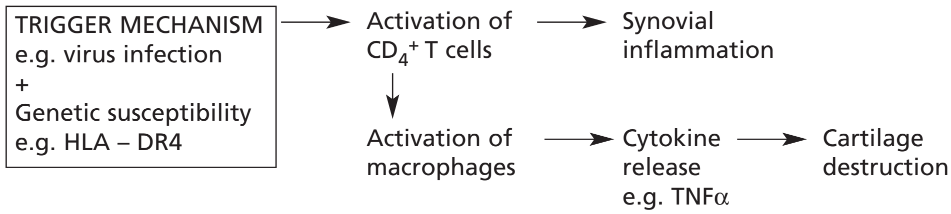
Late





RHEUMATOID ARTHRITIS (RA)

Rheumatoid arthritis is an autoimmune disease, with no single provoking factor. A possible hypothesis is:



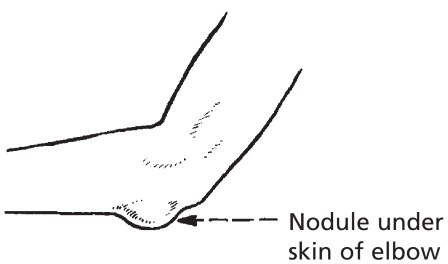
Joint destruction is due to a complex cascade of cytokines, inflammatory cell interaction, and alteration of activity of chondrocytes, osteoblasts and osteoclasts.

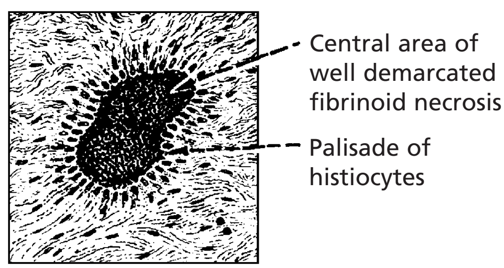
Modern therapy directed against TNFα suppresses disease activity and stops joint destruction.

Rheumatoid factors
These are antibodies, mainly of IgM and IgG class, which are directed against the patient's IgG, and may form immune complexes which may contribute to the joint inflammation. Patients in whom these autoantibodies can be found in the serum are described as seropositive. Around 85% of RA patients are seropositive.

The systemic nature of the disease is illustrated by inflammatory processes affecting the connective tissues at other sites.

1. Rheumatoid nodules occur under the skin at pressure points, particularly in the forearms and elbow joints in 1/5 of cases. They range in size up to a few centimetres in diameter. The histological appearance is striking.





2. The lung may show interstitial pneumonia sometimes with rheumatoid nodules. In coal miners, the mixture of coal dust and collagen gave characteristic radiological and pathological appearances – Caplan's nodules.
3. Necrotising arteritis is a serious complication in a few cases.
4. A mild interstitial myocarditis, polymyositis or neuritis may be seen in some cases. Serosal inflammation, e.g. pericarditis and pleurisy, are common.
5. Particularly in juvenile rheumatoid arthritis, lymphadenopathy is common and splenomegaly may cause hypersplenism – so-called Felty's syndrome.
6. Amyloid disease – may complicate long standing RA.

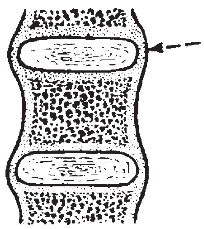
SERO-NEGATIVE ARTHRITIS

Ankylosing spondylitis (AS) is an arthritis affecting particularly the sacroiliac, costovertebral and vertebral joints, but peripheral arthritis is also seen.

Incidence: 0.05% of population
male:female; 3:1.

Age of onset: Young adults progressing into middle age.
Rheumatoid factor negative.

The disorder is, like RA, an active chronic arthritis, but differs in that it may cause osseous ankylosis (bony union), so that no movement of the affected joints is possible.



Bony union on the periphery of the intervertebral discs gives the characteristic radiological appearance – bamboo spine.

Aortitis leading to aortic incompetence and uveitis may be seen.

Psoriatic arthritis affects the axial and peripheral joints. Typically the distal interphalangeal joints are involved and the adjacent nails are affected.

Reiter's syndrome: This is a syndrome of polyarthritis, urethritis and uveitis following infections, e.g. chlamydia, yersinia and salmonella. The detailed mechanisms are unclear.

HLA association. Ankylosing spondylitis, psoriatic arthritis and Reiter's syndrome are associated with HLA-B27 (>95% in AS). Genetic susceptibility is an important factor predisposing to the arthritis.

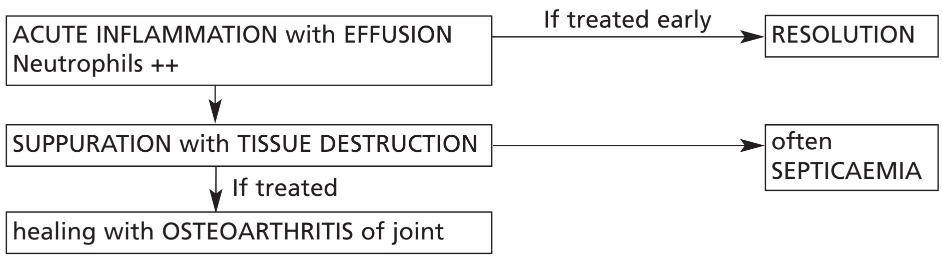
No such association with HLA-B27 is evident with RA, which however shows an association with HLA-DR4, twice that of the general population.

	OSTEOARTHRITIS	**RHEUMATOID ARTHRITIS**
Type of disorder	Degenerative	Inflammatory
Site of initial damage	Articular cartilage	Synovial membrane
Age	Late middle age +	3rd decade (any age)
Joints affected	Large weight bearing often single, pre-existing local factors in some cases	Small joints of hands and feet, multiple
Systemic disease	None ESR – normal Rheumatoid factor – absent	++ ESR ↑ Rheumatoid factor positive Secondary anaemia

INFECTIONS OF JOINTS

1. **Acute infective arthritis**

(a) Primary pyogenic haematogenous infection is now rare. It remains, however, a serious complication in joints already damaged. *S. aureus* is the common infecting organism. The essential changes are:



(b) Arthritis complicating **gonorrhoea** and **brucellosis**.
In both of these conditions, a polyarthritis may occur in the acute phase and, in a small number, continues as a low grade arthritis. The spine particularly is affected in brucellosis.

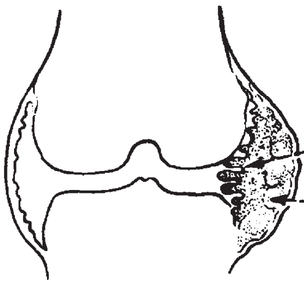
2. **Tuberculous arthritis**
In Western countries the incidence is low: a few cases arise complicating reactivated pulmonary tuberculosis in the elderly. If untreated, there is a low grade chronic inflammation with effusion and progressive destruction of tissues.
The diagnosis requires culture of joint fluid and/or biopsy when the typical histology of tuberculosis is seen.

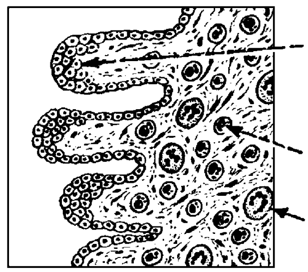
3. **Lyme disease** is a polyarthritis due to *Borrelia burgdorferi* transmitted by bites from deer ticks.

JOINT AND SOFT TISSUES – MISCELLANEOUS

Pigmented villonodular synovitis (PVNS) (tenosynovial giant cell tumour)

This may affect any synovial tissue, but the knee and hip joints are most commonly involved. There is a strong male predominance (age 20–50). The synovial membrane shows proliferation of brown pigmented large villi or rounded nodules.





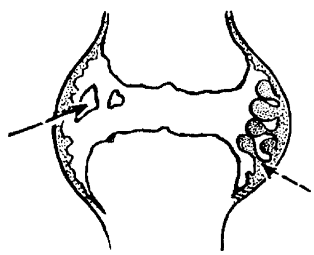
It is now thought to be neoplastic **but to all intents it never metastasises.**
The so-called benign giant cell tumour of tendon sheath is now considered to be a solitary variant of PVNS.
Similar but well-defined nodules are common in the fingers and toes.

SOFT TISSUE TUMOURS

These are dealt with on pages 123 and 124: 128–130.

LOOSE BODIES IN JOINTS

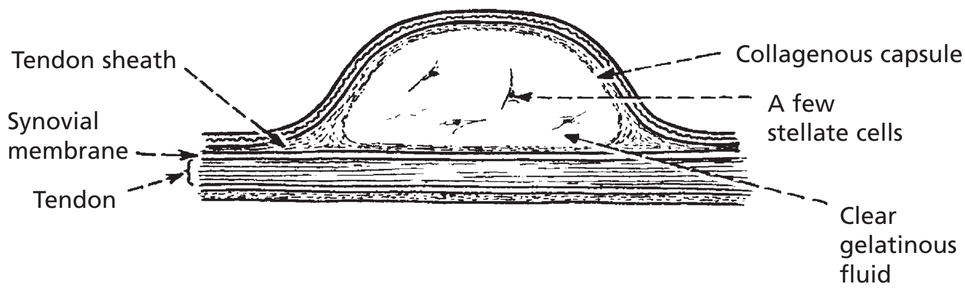
Loose bodies are usually found in diseased or damaged joints and their presence tends to aggravate any existing disease. Clinically, there is often recurrent 'locking' of the joint.



PARA-ARTICULAR TISSUES – MISCELLANEOUS

Bursae
These are synovial-lined spaces usually overlying bony prominences, e.g. the olecranon and patella, and often connected with adjacent joint spaces. They may become inflamed (bursitis).

Ganglion
This is a swelling which forms in relation to joint synovium or more usually, tendon sheath due to myxoid degeneration. It is not lined by synovium. Ganglia are classically seen around the wrist.



This type of myxoid cystic degeneration may occur at other less prominent sites, e.g. within the cartilagenous menisci of the knee.

Dupuytren's Contracture. See page 124.

COLLAGEN DISEASES

This term describes a group of multisystem diseases, many autoimmune in origin.

The group includes rheumatoid arthritis (RA); systemic lupus erythematosus (SLE); systemic sclerosis; polyarteritis nodosa (PAN) and dermatomyositis.

Systemic lupus erythematosus (SLE)
SLE is a chronic relapsing and resulting disease characterized by damage to multiple organs but especially the skin, joints, kidneys and central nervous system. It is much commoner in females.

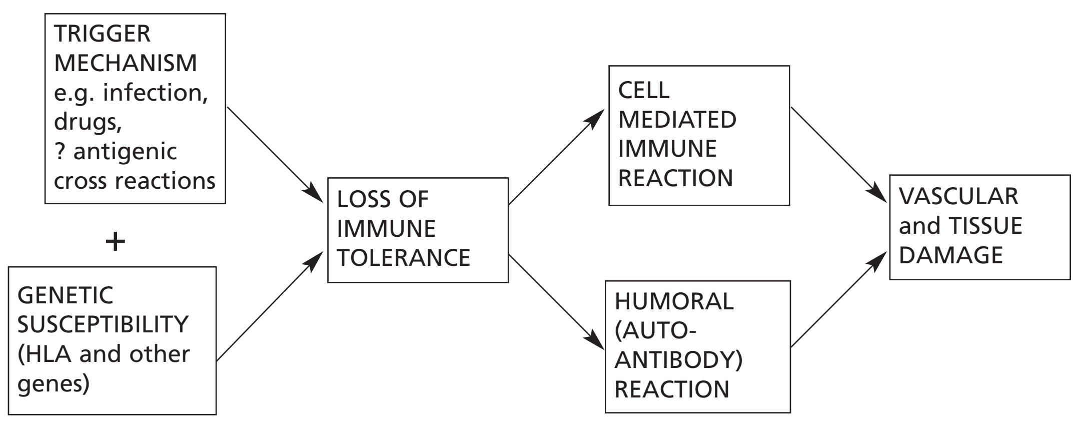
SLE is an autoimmune disorder. There are antibodies directed against cellular constituents, e.g. antinuclear, anti-DNA. These autoantibodies damage tissue by a type III hypersensitivity reaction (p.102).

Organs affected:

Kidney	–	often there is glomerulonephritis
Skin	–	erythema of the bridge of the nose and cheeks (malar rash); made worse by sunlight
Joints	–	synovitis
Brain	–	focal neurological signs may develop due to vasculitis
Heart	–	pericarditis, myocarditis, endocarditis (Libman–Sacks)
Lungs	–	pleuritis.

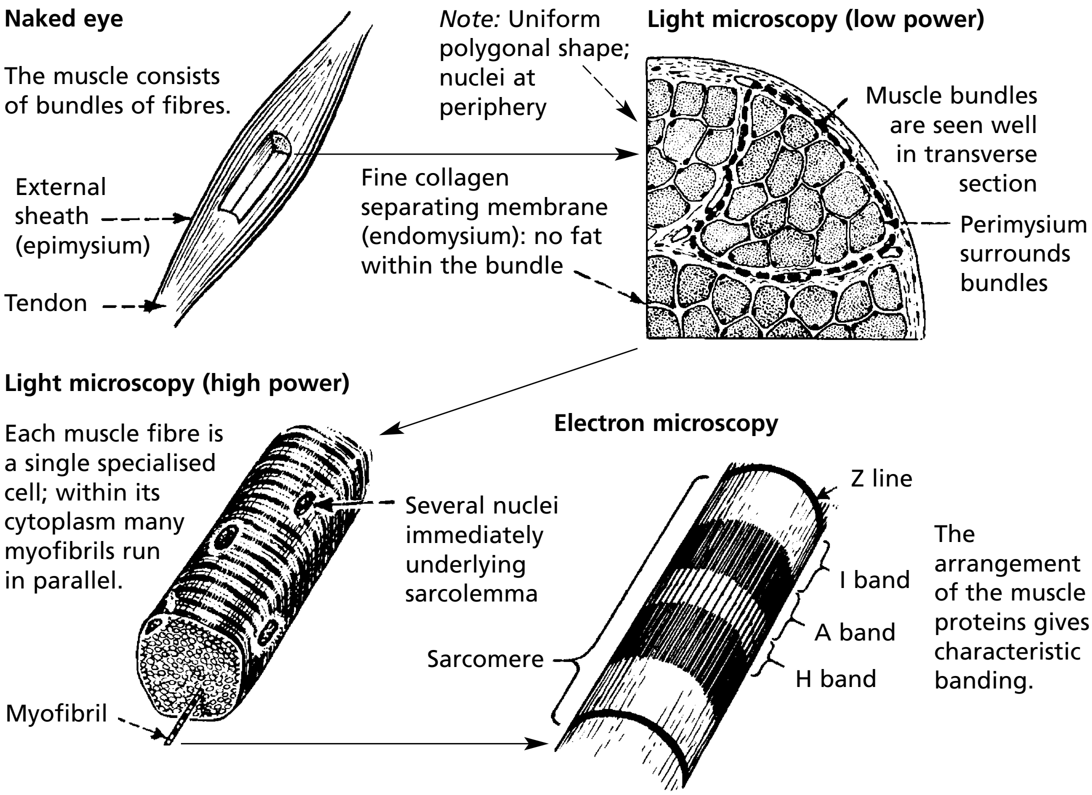
Systemic sclerosis (scleroderma)
This is a rare, slowly progressive disease in which there is gradual fibrosis of various organs including the skin (face and hands), gastrointestinal tract, heart and lungs. It is associated with Raynaud's disease. The basic abnormality is in the small blood vessels, which show sclerosis with intimal thickening. The change is associated with fibrosis of the surrounding tissues. Auto-antibodies, typically against nuclear components, are often found.

In collagen diseases, the basic mechanisms are inflammatory and are mediated by autoimmune processes. The inflammatory damage is very variable in its severity, its site of predilection and even its local effects. Multiple factors, of which inherited susceptibility and resistance are important, are involved. The following diagram illustrates the basic mechanisms.



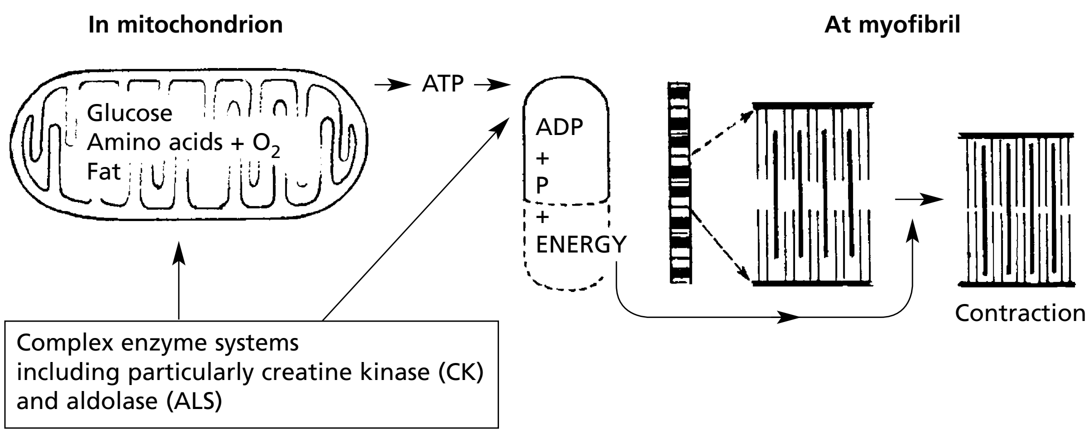
SKELETAL MUSCLE

Anatomy



MUSCLE CONTRACTION

The basic mechanism is as follows:



SKELETAL MUSCLE

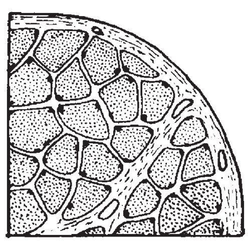
There are 3 types of muscle fibre, related to differences in functional activity.

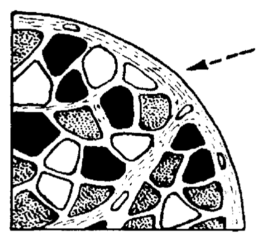
	Type of contraction	Location	Myoglobin	Mitochondria	Metabolism
Type I (red muscle)	SLOW twitch, FATIGUE RESISTANT	POSTURAL MUSCLES	+++	+++	AEROBIC
Type IIa (red muscle)	FAST twitch, FATIGUE RESISTANT	e.g. in LEGS of SPRINTERS	+++	+++	AEROBIC
Type IIb (white muscle)	FAST twitch, FATIGUABLE	ARM MUSCLES	+	+	ANAEROBIC

Note: Most muscles are a mixture of the 3 fibre types, but the proportion varies according to the function of the muscle.

In section, the three fibre types are identified by their ATPase activity.

Normal muscle stained H & E





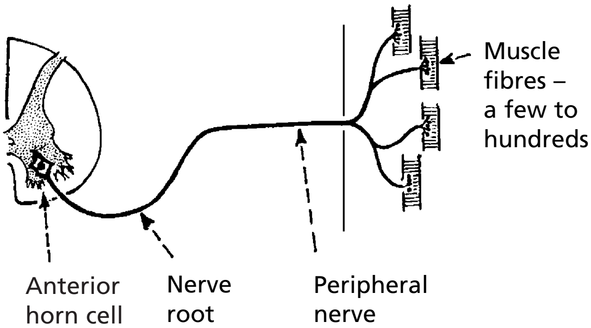
Normal muscle stained for ATPase activity

Type I = black
Type IIa = white
Type IIb = stipple
Note random mosaic pattern.

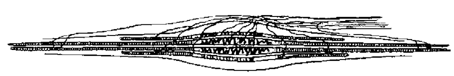
It is of interest that the muscle fibre function is not intrinsic but is conditioned by its type of nerve supply: any single anterior horn cell innervates fibres of only one type.

MUSCLE INNERVATION

The motor unit consists of:
a single lower motor neurone (**LMN**) — and the muscle fibres it supplies.



Muscle spindles

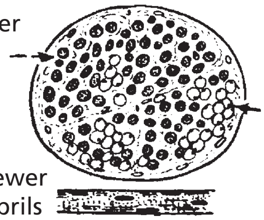


Muscle spindles are bundles of specialised fibres which control and refine muscle contraction and are important for proprioception. They are separately innervated from the surrounding fibres.

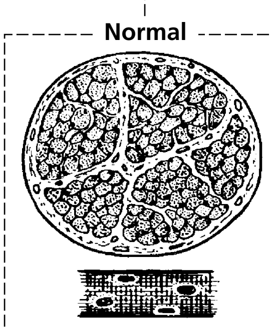
ATROPHY AND HYPERTROPHY

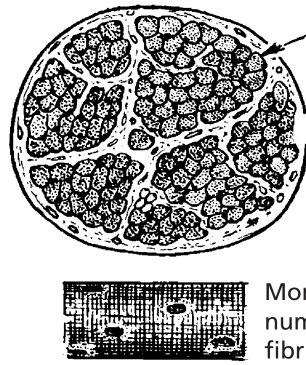
Generalised disuse atrophy occurs as a result of prolonged immobilisation in bed. Local atrophy follows immobilisation due to joint disease or after bone fractures.

Hypertrophy of muscle tissue in response to increased work load is well seen in athletes.



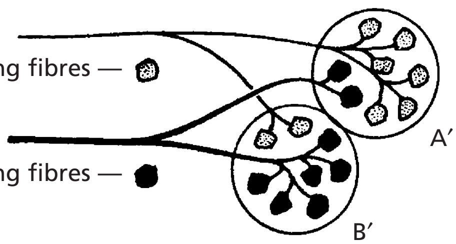
Note: Atrophy may be partially masked by increased fat in the septal tissues.





NEUROGENIC ATROPHY

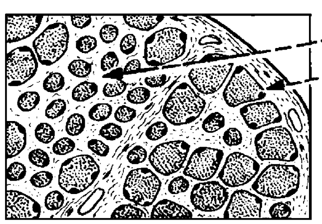
This form of atrophy is seen when the nerve supply is damaged. The distribution of nerve fibres within the muscle is important and is represented diagrammatically in respect of two motor units: A and B.



Note that while A and B respectively innervate the majority of fibres in bundles A′ and B′, there is overlap between bundles. Since many axons supply a muscle the overlap is considerable.

Apart from complete traumatic section of a peripheral nerve, it is unusual for all motor fibres to a muscle to be destroyed. Both the basic pattern of innervation and the variations in nerve fibre damage are reflected in the histological appearances in the denervated muscle.

1. **Pattern of atrophy**



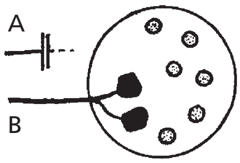
Groups of atrophic denervated fibres with adjacent groups of normal fibres.

NEUROGENIC ATROPHY

2. **Re-innervation**

In an area of denervation, the terminal axonal branches of intact neurones sprout and can re-innervate the atrophic fibres. The effects of denervation and re-innervation are shown in a muscle bundle supplied by 2 axons A and B.

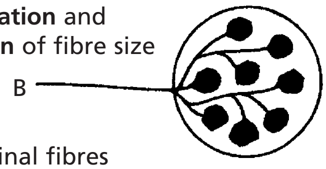
Denervation of A



Fibres supplied by A atrophy

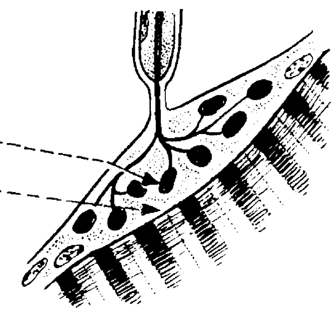
Fibres supplied by B remain normal

Re-innervation and **restoration** of fibre size



The terminal fibres of B now sprout and innervate the atrophic fibres which are restored to normal size.

MYASTHENIA GRAVIS



The **MOTOR END-PLATE** is the specialised neuromuscular junction situated at the middle of each muscle fibre. The nervous impulse causes release of **ACETYLCHOLINE** at the specialised nerve endings – depolarisation at this site is the stimulus to contraction. The sarcolemma at this site contains **CHOLINESTERASE**.
In MYASTHENIA GRAVIS, young females are most affected with muscle weakness and early fatigue of the ocular and head and neck muscles particularly.

Antibodies to ACETYLCHOLINE RECEPTORS are present in 90% of cases, blocking the effect of acetylcholine at the motor end plate.

There is a strong association with THYMIC abnormalities. In young women this is usually *thymic germinal centre hyperplasia*: in middle aged males a *thymoma* may be present.

MUSCLE DAMAGE

(a) **Trauma and ischaemia**

Trauma and ischaemia may combine to cause necrosis of a mass of muscle and the effects may be serious.

Trauma + Ischaemia → NECROTIC MUSCLE →
- Excellent medium for bacterial growth – especially CLOSTRIDIA (Gas gangrene)
- Release of myoglobin and other muscle degradation products aggravates SHOCK

The latter situation is well exemplified in the CRUSH SYNDROME – classically seen in building collapse.

Victim trapped under heavy debris → Crushing and ischaemic damage to thigh muscles → Released after several hours → Circulation restored through lower limbs → Massive release of myoglobin → Aggravation of shock → ACUTE RENAL TUBULAR NECROSIS

Massive release of myoglobin → ACUTE RENAL TUBULAR NECROSIS

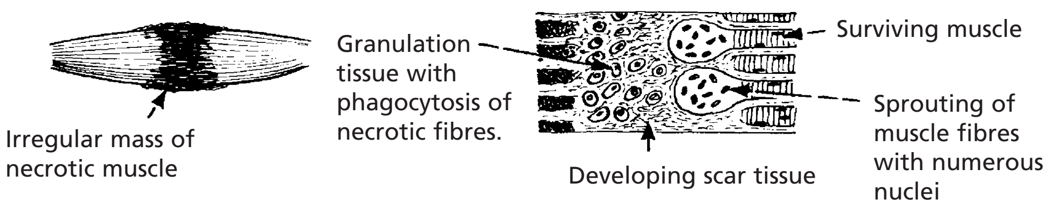
Repair of muscle damage

The inflammatory response is followed by organisation with removal of the dead muscle. There are two possible results:

(i) If the gap is not too great, regeneration effects restoration to normal.



(ii) If the gap is too great, scar tissue prevents the regeneration.



(b) **Inflammation**

Pyogenic infections of muscle are uncommon but abscess formation may follow intramuscular injections.

Viral myositis

A true myositis with focal necrosis of fibres, lymphocyte and macrophage infiltration can be caused by the Coxsackie group of viruses. The muscles of the upper thorax are particularly affected.

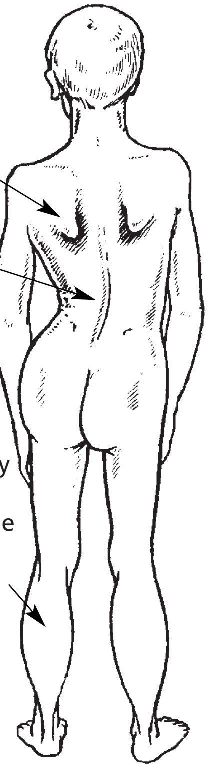
Parasitic myositis

In trichinosis, the parasitic larvae encyst in the interstitial tissues within muscles. The adjacent muscle fibres become necrotic; focal calcification is often a late sequel.

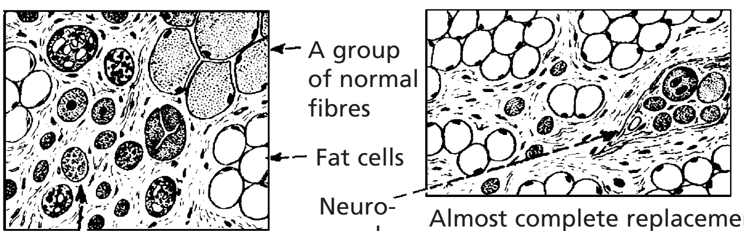
MUSCULAR DYSTROPHY

Muscular dystrophies are inherited diseases, causing muscle damage and weakness.

Duchenne Muscular Dystrophy
This is the commonest and most serious form.
Clinical features: Muscle weakness in early childhood; typically wheelchair-bound by 12 years of age and death by late teens or early twenties.
Pathology: The main features are
(1) muscle fibre necrosis and
(2) regeneration.
In time, fibres are atrophic and there is fibrosis and fatty replacement.



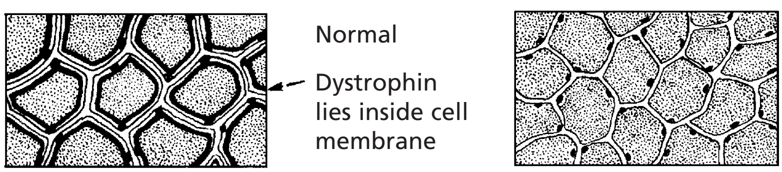
Biopsy shows:



Aetiology: This is an X-linked recessive disease occurring almost exclusively in boys. The dystrophin gene lies on the short arm of chromosome X.



Biopsy in early stages shows a lack of dystrophin using immuno-staining (anti-dystrophin antibodies).



Genetic screening for mutations of the dystrophin gene is now available.

Becker type muscular dystrophy is a milder form caused by mutation in the dystrophin gene resulting in diminished levels of the protein.
Other muscular dystrophies include the facio-scapulohumoral, limb girdle and myotonic dystrophy forms.

INHERITED MYOPATHIES

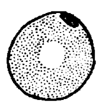
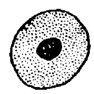
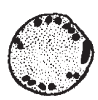
Specific metabolic defects

There is a group of genetic myopathies with specific biochemical or morphological abnormalities.

In some, the inborn error of metabolism is generalised and includes muscle; in others it is confined to the muscle fibre. Some examples will be given:

(1) **Glycogen storage**	(2) **Lipid metabolism**	(3) **Periodic paralysis**
Type 2 (Pompe) – deficiency of acid maltase Type 5 (McArdle) – muscle phosphorylase Type 7 – phospho-fructokinase (PFK)	Defect in free fatty acid transport into and utilisation within fibre. (a) carnitine palmityl transferase (CPT) (b) muscle carnitine deficiency	Associated with hypo- and hyperkalaemia – the muscle defect is a vacuolar degeneration of the sarcolemma

(4) **Morphological abnormalities**

(a) *Mitochondrial*	(b) *Others*	
Large or increased numbers of mitochondria – abnormal oxidative processes	(i) Central core myopathy  Central area is abnormal	(iii) Centronuclear myopathy  Nucleus in middle of cell
	(ii) Rod body myopathy (nemaline)  Rods of tropomysin under sarcolemma	(iv) Disproportion of fibre types I and II

These myopathies vary in age of onset, clinical presentation and prognosis.

A further rare but interesting autosomal dominant genetic abnormality of muscle is malignant hyperpyrexia. In this condition the administration of a general anaesthetic precipitates acute muscle damage. Clinically, there is very high fever, muscle stiffness, cyanosis and acidosis very often resulting in death.

ACQUIRED MYOPATHIES

Inflammatory myopathies – polymyositis and dermatomyositis – are two similar **inflammatory** disorders of muscle.

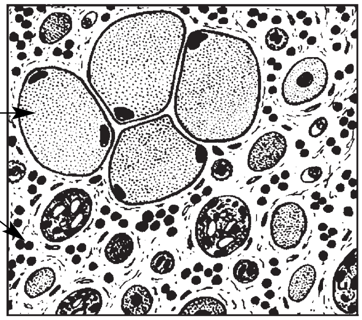
POLYMYOSITIS – occurs in both sexes and at any age, but especially in middle age. It is characterised by muscle pain and weakness – especially of proximal muscle groups. Progress is variable – deterioration may be rapid or slow.

DERMATOMYOSITIS – has similar muscle changes and also skin lesions often on the face and hands. In adults, dermatomyositis may herald malignancy – often bronchial carcinoma – and there is often evidence of other connective tissue diseases e.g. rheumatoid arthritis.

Pathology:

Muscle fibres show damage varying from atrophy to necrosis and some hypertrophied fibres are seen.

There is a lymphocytic infiltrate.



Aetiology

These are both autoimmune diseases although the precise details differ. Polymyositis is a T cell mediated attack on muscle fibres, while dermatomyositis is an immune complex disorder with vascular damage.

OTHER MYOPATHIES

In any wasting disease, loss of muscle with weakness is seen.

Primary condition

Chronic infection
Malabsorption
Cancer
Endocrine disorder
Extreme old age

→ Generalised CATABOLISM

→ The protein of muscle is particularly affected

→ Loss of muscle bulk; fibres smaller with nuclei closer together; muscle fibre loss – predominantly type II.

Myopathy is seen in acromegaly, hyperthyroidism, hypothyroidism, hyperaldosteronism (due to hypokalaemia), hyperparathyroidism and in corticosteroid excess.

In alcoholics and a variety of drugs in addition to corticosteroids, e.g. chloroquine, vincristine; and in vitamin D deficiency.

MUSCLE DISEASES – DIAGNOSIS

Accurate diagnosis of muscular weakness and atrophy is important since there is considerable variation in prognosis and management of these disorders, although often there is no treatment.

A diagnosis is usually reached from a synthesis of the information obtained from investigations under three headings:

1. **General clinical features** e.g. *family history, age of onset, distribution of muscle weakness and rate of progress.*
2. **Special investigation of neuromuscular electrical activity.** The rate of motor and sensory nerve conduction can be measured electrically.

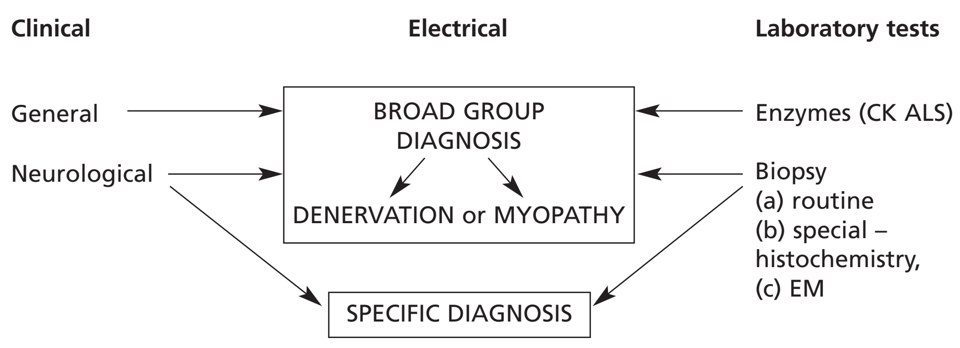
The ELECTROMYOGRAM records the activity of groups of muscle fibres and even of individual fibres (usually fine needle electrodes). The pathological changes are reflected in variations of the electrical potential within the muscle during various types of activity.

These methods distinguish primary myopathies, including myotonias, from denervation atrophy.

3. **Laboratory tests**
   (a) *MUSCLE BIOPSY*. The motor unit area of a moderately weak muscle is chosen (end-stage muscle should not be taken). Special precautions must be taken to minimise artefacts. Histological examination of frozen muscle, allowing histochemical tests, will usually distinguish the broad groups of disorders and identify the occasional rare myopathy with specific morphological features.

   EM examination and biochemical analysis may identify specific disorders.

   (b) *SERUM ENZYMES*. In the myopathies where muscle fibres are being destroyed, increased levels of creatine kinase (CK) and aldolase (ALS) are found.



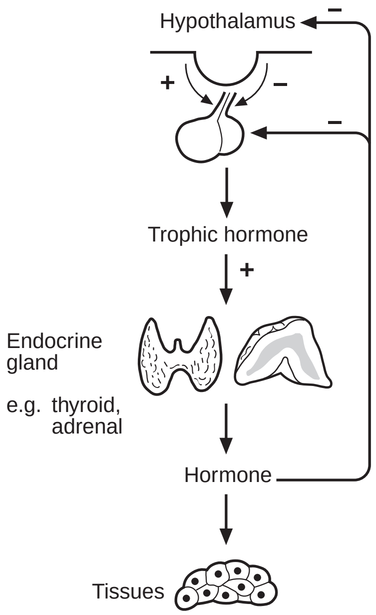
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CHAPTER 16

ENDOCRINE SYSTEM

ENDOCRINE DISEASES

Most endocrine glands are controlled by hormones produced in the anterior pituitary, themselves under control of substances produced in the hypothalamus. A variety of stimuli control pituitary and hypothalamic hormone release, especially feedback control from hormone levels from the target glands. Levels of pituitary hormones show a circadian rhythm.



Endocrine diseases can be broadly classified as:

Hormone excess
– primary overproduction by gland
– secondary to excessive trophic hormone

Hormone deficiency
– primary underproduction by gland, e.g. due to inflammation, post surgery
– secondary to insufficient trophic hormones

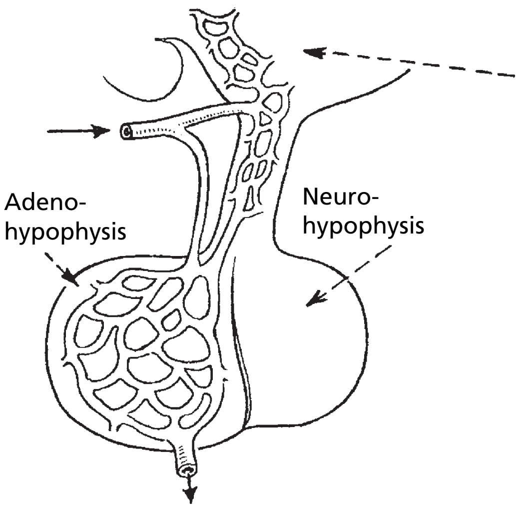
Hormone resistance
– target organ resistance
– failure to activate hormone

Effects of non-functioning tumours
– local pressure and invasion
– metastatic disease.

PITUITARY GLAND

The pituitary has two parts; the anterior (adenohypophysis) and the posterior (neurohypophysis).

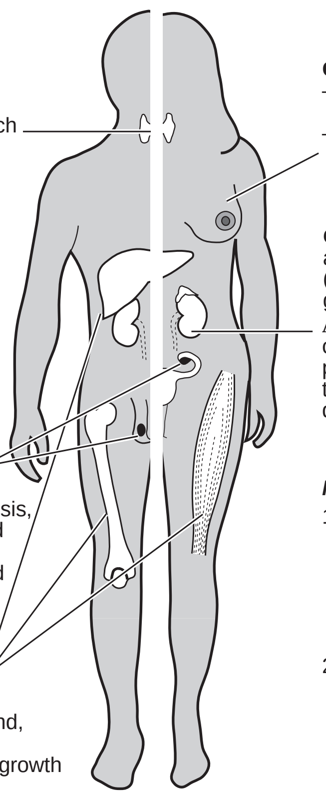
Anterior pituitary (adenohypophysis)



The blood supply is via a portal system from the hypothalamus bringing peptides which stimulate or inhibit pituitary hormone production. The cells producing each hormone can be identified by immunohistochemistry (for stored hormone) or in situ hybridisation (for mRNA).

Posterior pituitary

This is composed of neural tissue and secretes two hormones made in the hypothalamus (oxytocin and antidiuretic hormone).



Note

1. ACTH (39 amino acids long) is synthesised as part of a large molecule proopiomelanocortin (POMC) from which other molecules including melanocyte stimulating hormone (MSH) are derived.

2. Hypothalamic releasing hormones have been found for TSH (TRH), LH/FSH (GnRH), ACTH (CRH) and GH (GHRH); somatostatin inhibits release of GH.

PITUITARY HYPERFUNCTION

In most cases, this is associated with PITUITARY ADENOMA.

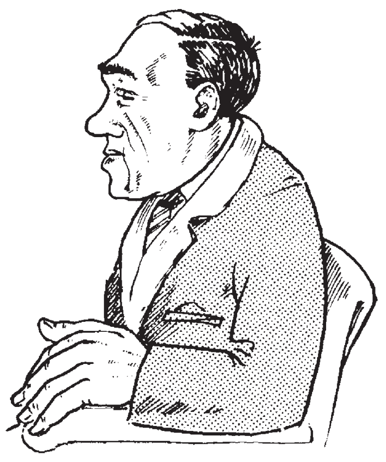
Pituitary adenomas are divided on the basis of size into MACROADENOMAS (>10 mm) and MICROADENOMAS (<10 mm).

Small tumours present only if they produce excess hormones, while larger tumours may cause pressure effects (e.g. on optic chiasma, page 141) or with hypopituitarism due to destruction of normal pituitary. Occasionally haemorrhage into a pituitary adenoma causes raised intracranial pressure (PITUITARY APOPLEXY).

Gigantism and acromegaly
These are both the result of excess production of growth hormone by a somatotroph (acidophil) adenoma. Gigantism arises in children before the epiphyses have fused; acromegaly occurs in adult life.

Gigantism
The excess growth hormone induces skeletal growth, the bones retaining their normal shape and relative proportions. Fusion of epiphyses is delayed, but eventually occurs and the features of acromegaly appear.

Acromegaly
There is overgrowth of bone and soft tissue.



Clinical signs
Features coarsened: nose enlarged.
Prognathic (projecting jaw).
Irregular bone formation – interferes with joint function – leads to osteoarthritis.
Limbs enlarged.

Pain due to nerve compression is common. Glucose tolerance is diminished and diabetes occurs in 10%. High blood pressure with cardiac hypertrophy and extensive atheroma is common, and the patient may die in cardiac failure. There is a 2–3 fold increased risk of colonic cancer.

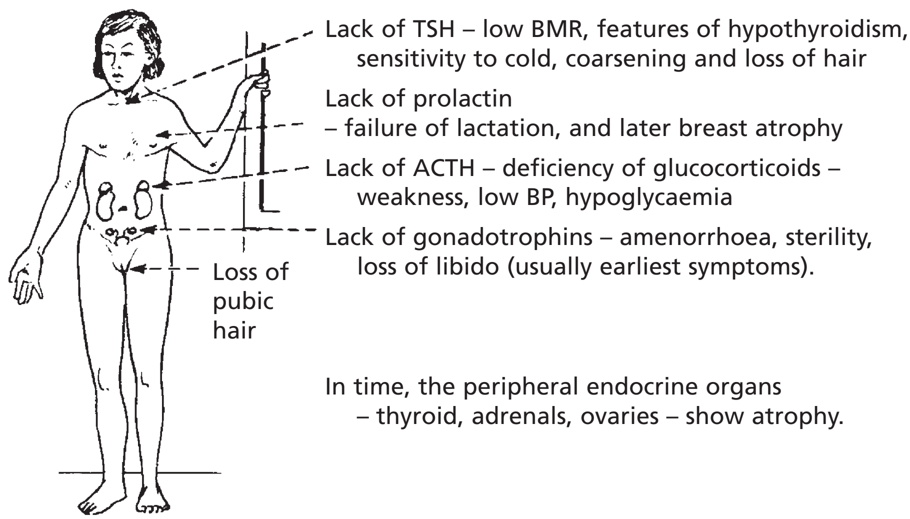
HYPERPROLACTINAEMIA
Prolactin secreting adenomas are often small. They cause amenorrhoea, infertility and occasionally galactorrhoea in younger women, but are usually asymptomatic in older women and men.

CUSHING'S SYNDROME is frequently due to an ACTH secreting adenoma when it is known as Cushing's disease. The effects are described on p.634.

HYPOPITUITARISM

Failure of pituitary secretion may affect one or several hormones. Causes include:
(a) Pituitary tumour.
(b) Pituitary surgery/cranial irradiation.
(c) Head injury.
(d) Hypothalamic dysfunction, including craniopharyngioma.
(e) Sheehan's syndrome: is used as an example. It is still an important cause where obstetric services are poor.

This syndrome occurs in women and is due to ischaemic necrosis of the pituitary following post-partum haemorrhage. The normally low pressure in the pituitary portal vascular supply increases the susceptibility of the gland. The results vary with the extent of necrosis and may include the following:



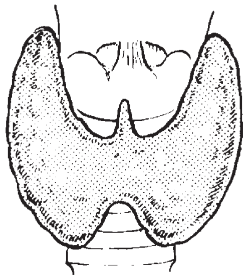
In childhood, growth hormone deficiency is a cause of dwarfism. Skeletal growth is diminished with retarded sexual development but normal intelligence. Hypothalamic GHRH deficiency may be responsible.

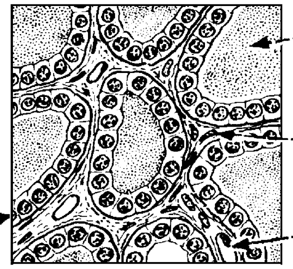
Note: Some individuals treated with human growth hormone have developed Creutzfeld–Jacob disease (p.555).

In adults, GH deficiency leads to lethargy, diminished muscle mass, obesity and premature atheroma.

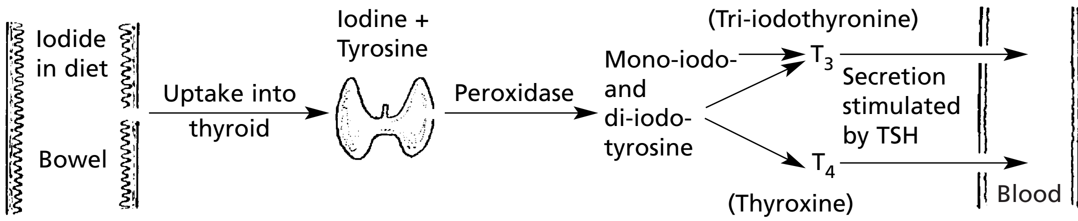
Inflammation of the pituitary gland
Apart from involvement in acute meningitis, inflammation, acute or chronic, is uncommon. Tuberculosis, syphilis and sarcoidosis all rarely occur.

THYROID GLAND – UNDERACTIVITY





The thyroid gland is under the control of the pituitary thyroid-stimulating hormone (TSH p.623).

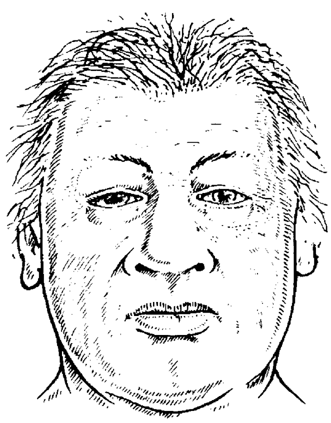


T_4 can be regarded as a prohormone, which is converted to active T_3 by deiodination in liver, muscle and kidney.

THYROID HYPOFUNCTION

Insufficient thyroid hormone is produced, resulting in myxoedema in adults and cretinism in children.

Adults – MYXOEDEMA



Clinical signs

Basal metabolic rate reduced, weight gain.
Body temperature falls, cold intolerance.
Lethargy and apathy.
Appetite reduced.
Constipation.
Respiratory and heart rates reduced.
Diminished libido.
Lack of ovulation.
Skin thickened, non-pitting oedema due to increase in mucopolysaccharide ground substance.
Hair brittle, dry and falls out.
Blood cholesterol is raised.
TSH secretion is increased.
T_3 and T_4 blood levels low.

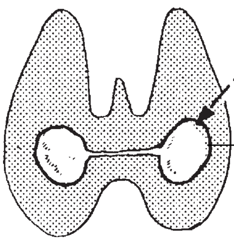
THYROID GLAND – UNDERACTIVITY

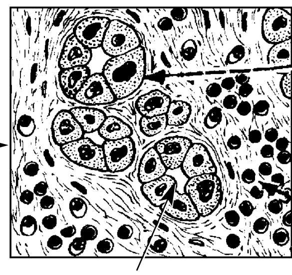
Myxoedema (*continued*)

Causes

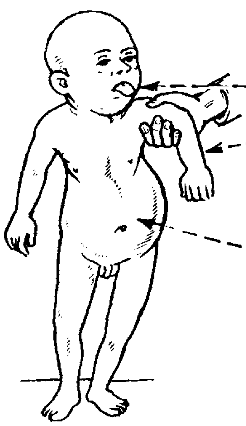
1. Autoimmune thyroiditis
(a) Atrophic form – so-called **primary myxoedema** – the commonest cause of hypothyroidism
(b) **Hashimoto's disease.**
2. Severe iodine deficiency.
3. Dyshormonogenesis – inborn errors in the formation of thyroid hormones.
4. Anti-thyroid drugs, e.g. lithium
5. Excessive surgical resection of thyroid gland.
6. Treatment with radioiodine.
7. Hypopituitarism → reduced TSH.

Pathological changes in primary myxoedema





Children – CRETINISM



Infants normal at birth, but abnormality appears within weeks.

Clinical Signs

Changes are irreversible unless treatment is given early.
Two forms are recognised:

(1) endemic and (2) sporadic cretinism.

THYROID GLAND – OVERACTIVITY

Endemic cretinism
This occurs in districts where goitre is common due to iodine deficiency. The infantile thyroid is usually enlarged and nodular. Histologically, there are hyperplastic foci containing colloid which compress the intervening tissue. The incidence of this disorder has reduced following addition of iodine to salt.

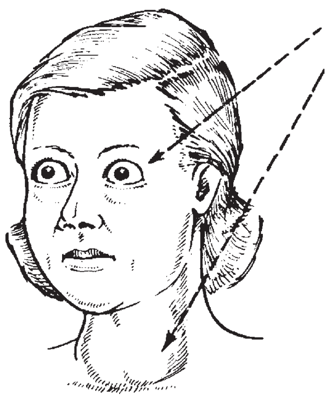
Sporadic cretinism
This is usually due to congenital hypoplasia or absence of the thyroid. Deaf mutism is often present.

Dyshormonogenesis
In this condition, cretinism is due to a congenital familial recessive enzyme defect leading to inability to complete the formation of thyroid hormone. The thyroid gland is enlarged and shows epithelial hyperplasia. TSH is increased.

THYROID HYPERFUNCTION
Excessive quantities of circulating thyroid hormone (T_3 and T_4) cause thyrotoxicosis. Three types of thyroid lesion can give rise to thyrotoxicosis.

1. Graves' disease (exophthalmic goitre) >80%.
2. Toxic nodular goitre 10%.
3. Toxic adenoma <5%.

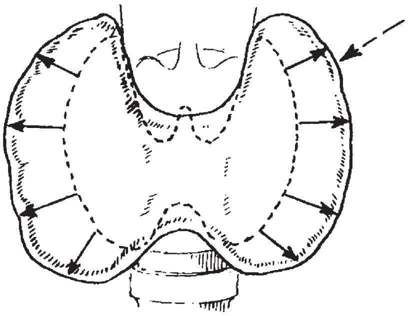
Graves' Disease (Exophthalmic goitre)

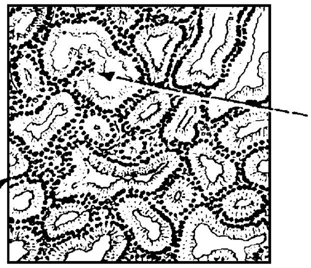


Clinical signs:
Exophthalmos.
Prominent thyroid.
BMR increased.
Skin warm and sweaty: heat intolerance.
Weakness, hyperkinesia and emotional instability.
Loss of weight.
Glucose tolerance diminished, glycosuria.
Rapid pulse.
Cardiac arrhythmia, especially atrial fibrillation, and heart failure in older patients.
TSH low.

THYROID GLAND – OVERACTIVITY

Graves' disease





In some cases there are foci of thyroiditis with lymphocytes and plasma cells.

Other changes: 1. Patches of myxoedema – usually on pre-tibial aspect of legs.
2. Exophthalmos, due to autoimmune damage to the eye muscles.

Aetiology: 1. Usually in females, peak 20–40 years.
2. More common in families showing high incidence of autoimmune disease, e.g. thyroiditis, pernicious anaemia.
3. The stimulation of the thyroid is due to an autoantibody (thyroid stimulating immunoglobulin/TSH antibody also known as TRAb) which reacts with and activates the surface receptor for TSH on thyroid epithelium. Cyclic AMP is formed and this stimulates hyperplasia of the epithelium and increased formation of thyroid hormone. With the increase in hormone, the blood TSH falls.

Toxic adenoma
Most adenomas are non-active; only a small proportion (1%) give rise to toxic symptoms. Most patients are women over 40 years.

There is usually only one large adenoma present. The histological features are of follicles which may be small or of normal size. Increased production of thyroid hormone by the adenoma, which is autonomous, causes a fall in TSH, and the remainder of the thyroid is inactive.

Toxic nodular goitre
This develops in some cases of non-toxic nodular goitre. Nodules of hyperplasia are interspersed with inactive tissue. The condition is more common over the age of 50 especially in women. Exophthalmos is absent. Cardiac arrhythmias and heart failure is common.

THYROID GLAND

Non-toxic goitre

This is a simple enlargement of the thyroid gland, not associated with increased secretion of thyroid hormone.

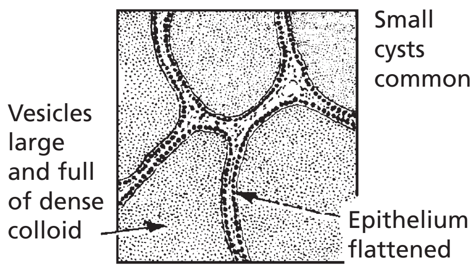
The gland is enlarged and pale pink. Two phases can be recognised:

(a) **Diffuse hyperplasia:** The gland consists mainly of small closely packed acini lined by columnar epithelium and containing a small amount of poorly stained colloid. Occasional intra-acinar papilliform epithelial projections may be seen.

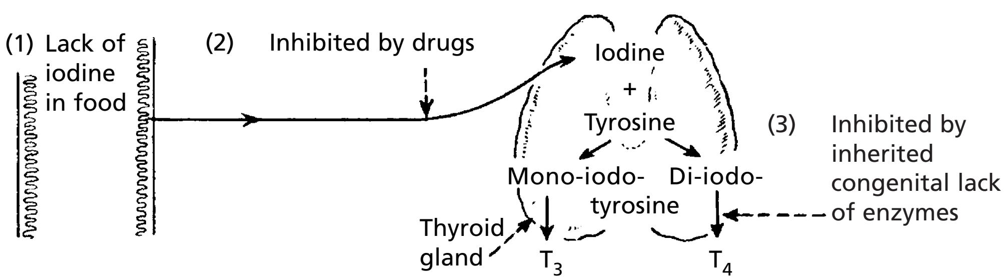
(b) **Nodular hyperplasia:** This is a later stage. Areas of marked hyperplasia cause atrophy of intervening parenchyma. It appears to be related to continuing severity of iodine deficiency.

Sometimes the enlarged gland is translucent and brown due to the large amount of stored colloid (colloid goitre).

This is common in women and appears at puberty or during pregnancy. There are usually no symptoms, but pressure symptoms develop if the thyroid is retrosternal, e.g. pressure on trachea causing stridor, pressure on recurrent laryngeal nerve → hoarseness.



Aetiology. In most regions the aetiology is unknown. Goitre is endemic in central areas of the world, mountainous regions remote from the sea – Switzerland, Himalayas, Andes, etc. There is a lack of iodine in the soil, hence in the food. Addition of iodine to salt has lowered the prevalence.



Mechanism of goitre production

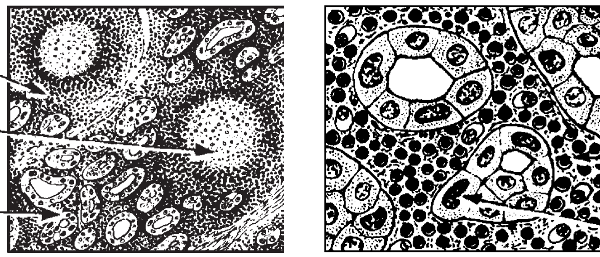
Lack of iodine ⟶ Deficient production of thyroid hormone ⟶ ↑TSH secretion ⟶ Enlargement of thyroid to extract maximum amount of iodine from blood

THYROID GLAND

AUTOIMMUNE THYROIDITIS

This type of disease is associated with the appearance of thyroid antibodies in the blood and inflammation with lymphocytes and plasma cells in the thyroid gland. There is an associated risk of development of non-Hodgkin's lymphoma in each.

1. **Hashimoto's thyroiditis (lymphadenoid goitre)**
   This is the most distinctive type of autoimmune thyroid disease, and the changes are widespread.



Clinical effects: The patient may be euthyroid but eventually may develop hypothyroidism. Any attempt to reduce the size of the goitre by surgery inevitably causes hypothyroidism.

In a small proportion of cases the patient has thyrotoxicosis in the early stages of the disease due to overactivity of the gland.

2. **Primary Myxoedema**

   Antibodies to thyroid hormones and epithelium are found in this disease (p.626).

3. **Focal thyroiditis**

   This extremely common form of autoimmune disease is usually asymptomatic, but partial thyroidectomy may precipitate hypothyroidism. The concentration of antibodies in the plasma is always low.

   Patients with autoimmune thyroiditis often have other organ-specific antibodies, e.g. gastric, adrenal etc., and pernicious anaemia and adrenal insufficiency may occur.

4. **Graves' disease** (p.628).

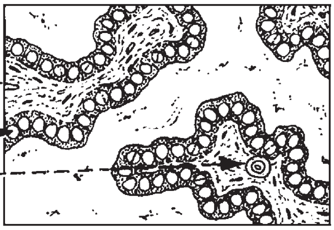
TUMOURS OF THYROID

Follicular Adenoma
This fairly common benign tumour is usually single and is encapsulated with compression of the surrounding gland. Very occasionally there is hypersecretion with thyrotoxicosis. Degenerative changes including haemorrhage into the tumour are common.

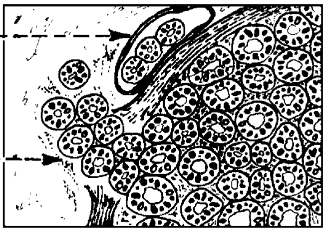
MALIGNANT TUMOURS are common. Five forms are recognised:

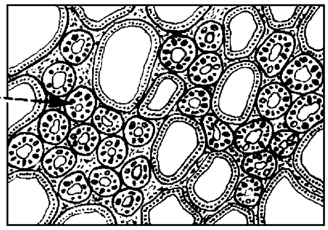
1. ***Papillary carcinoma*** 60–70%. This affects particularly young women: the tumours are usually small and may be multiple within the thyroid. They metastasise readily to local lymph nodes and the first clinical sign may be an enlarged cervical lymph node containing metastatic papillary tumour. Remote spread is unusual.

The histological appearances are typical:



2. ***Follicular carcinoma*** 15–20%. These tumours have their highest incidence in women over middle age. They present in 2 forms:
   (a) Minimally invasive, well encapsulated and can only be differentiated from adenoma by invasion of the capsule and/or veins.
   (b) As a tumour of varying degrees of follicular differentiation, which spreads widely in the thyroid and invades venules.





Blood spread particularly to BONES and LUNGS is usual in follicular carcinoma.

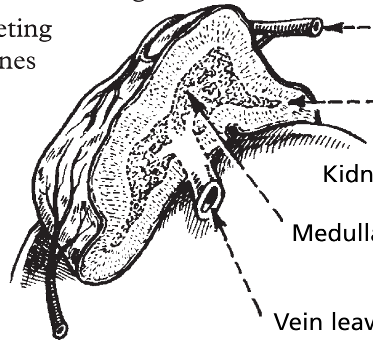
3. ***Medullary carcinoma*** 5–10%. This is a rare tumour arising from the calcitonin-producing cells of the thyroid. Blood calcitonin is high. In addition, there may be production of other hormones resulting in a carcinoid or Cushing's syndrome. There is a familial form in which there are multiple tumours of a number of endocrine organs (MEN 2, p.643).
4. ***Anaplastic carcinoma*** This occurs in the elderly and may cause stridor. Distant metastases are common. The prognosis is very poor.
5. ***Lymphoma*** B cell lymphoma occasionally arises in long-standing autoimmune thyroiditis (particularly Hashimoto's disease).

ADRENAL GLAND

The adrenal gland has two parts and several functions.

There are:

1. Cortex, secreting – glucocorticoids
   – mineralocorticoids
   – androgens
2. Medulla, secreting
   – catecholamines



Mineralocorticoids

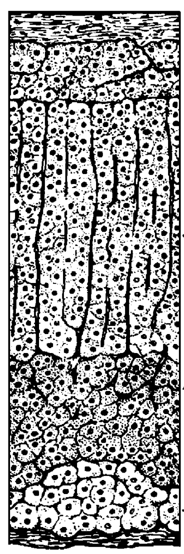
The main one is aldosterone. It is involved with the renin-angiotensin system and ADH in the maintenance of blood volume. The mechanism is as follows:

Fall in renal output of Na → Stimulation of juxtaglomerular system

Fall in renal perfusion → Stimulation of juxtaglomerular system

Stimulation of juxtaglomerular system
↓
Renin secretion
↓
Angiotensin formed in blood
↓
Aldosterone secretion
↓
Increase in renal absorption of sodium → Retention of fluid

Increased tubular secretion of K^+



Zona fasciculata + Zone reticularis: **Source of gluco-corticoids + androgens**

→ Metabolic effects, e.g.:
- protein catabolism
- increased gluconeogenesis
- cardiovascular effects
- anti-inflammatory plus immunosuppresive effects

→
- initiation of puberty
- libido (in females)

Medulla (chromaffin cells)
↓
Source of catecholamines

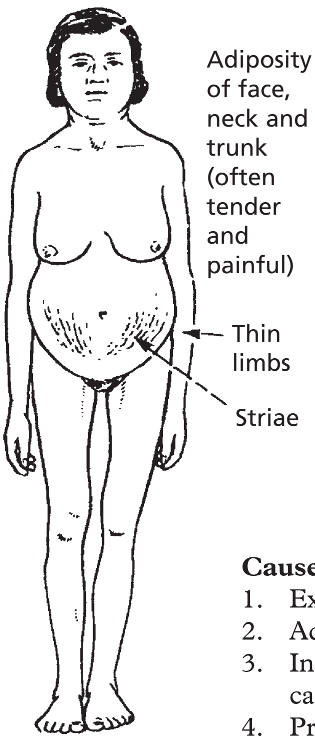
Adrenaline
↓
β-adrenoreceptors
↓
↑ Heart rate
Vasodilatation
Insulin resistance

Noradrenaline
↓
α-adrenoreceptors
↓
Vasoconstriction
↓
↑ Blood pressure

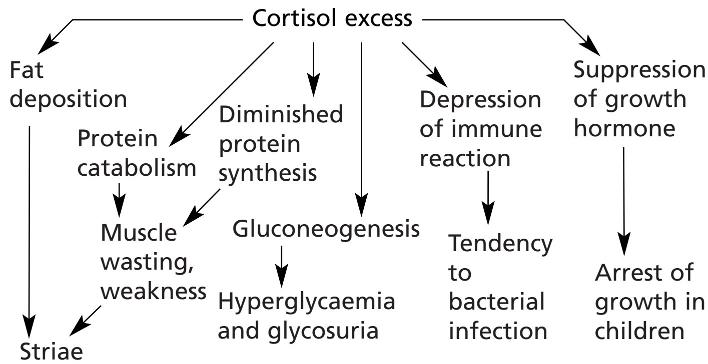
ADRENAL CORTEX – OVERACTIVITY

Overactivity manifests itself in three ways:

1. **Cushing's syndrome** (hypersecretion of cortisol) – CORTICOSTEROID EXCESS
This condition is commonest in women, but occurs also in men and rarely in children.



Clinical effects



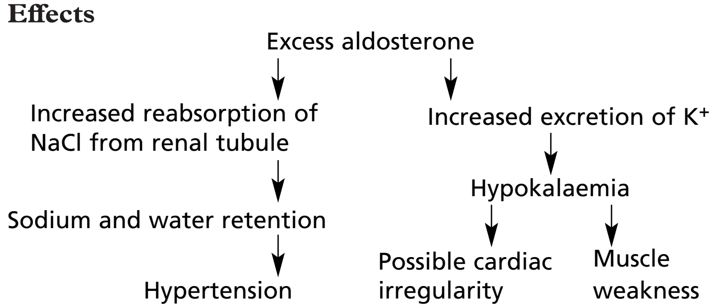
In addition: 1. Osteoporosis → kyphosis
2. Hypertension
3. Degree of virilism common in women.

Causes

1. Excessive secretion of ACTH by pituitary adenoma, 70%.
2. Adenoma or carcinoma of adrenal cortex, 20%.
3. Inappropriate secretion of ACTH e.g. by bronchial carcinoma, carcinoids, pancreatic tumours.
4. Prolonged administration of glucocorticoids or ACTH as therapy.

2. **Primary hyperaldosteronism** (Conn's syndrome) – MINERLOCORTICOID EXCESS
This is due to (~60%) or an adenoma (~35%) or hyperplasia of the zona glomerulosa.

Effects



Note: Secondary hyperaldosteronism is a consequence of any high renin state, e.g. renal ischaemia.

3. **Excessive sex hormone secretion** – ANDROGEN EXCESS
This can occur occasionally with an adrenal cortical adenoma; usually excessive androgens are secreted. (a) In children it causes precocious puberty; (b) In adult females – virilism, oligomenorrhoea.

ADRENAL CORTEX – HYPOFUNCTION

Adrenal cortical insufficiency may be due to panhypopituitarism or destruction of about 90% of the adrenal cortex. *Acute adrenal failure* is usually due to septicaemia, especially meningococcal (Waterhouse–Friderichsen syndrome).

Septicaemia → Endotoxaemia → Adrenal haemorrhage and necrosis

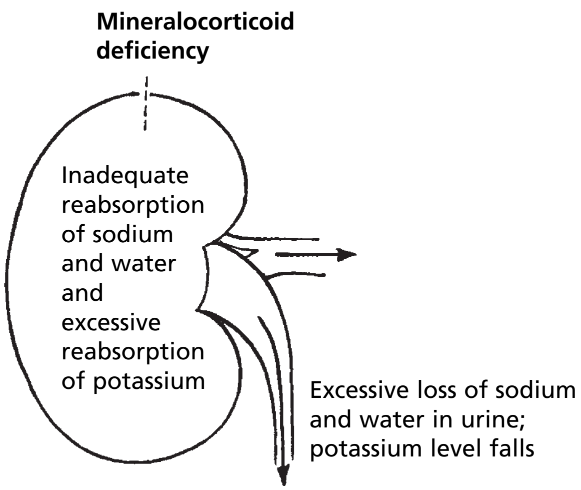
Endotoxaemia → Shock ← Adrenal haemorrhage and necrosis

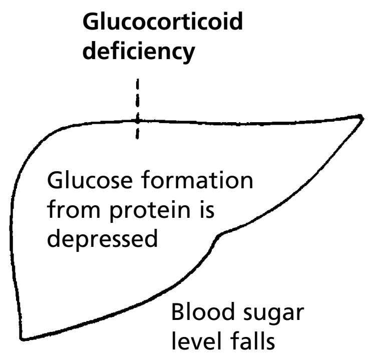
Chronic Hypofunction

Causes

1. Addison's disease. This is an autoimmune adrenalitis with humoral or cell mediated damage to the adrenal gland. It is responsible for at least 75% of cases.
2. Tuberculous destruction of adrenals – remains an important cause, especially in developing countries.
3. Pituitary failure.

Other autoimmune diseases affecting other endocrine glands are commonly associated with Addison's disease, e.g. thyroid, parathyroid disease, diabetes.





Other features

Muscular weakness and wasting.
Loss of weight.
Gastrointestinal upsets (vomiting, diarrhoea).
Anaemia.
Pigmentation of exposed and pressure areas of skin (↑ MSH).
Dehydration.
Crises occur especially if acute infection complicates the condition.

Administration of adrenal hormones restores individual to normal.

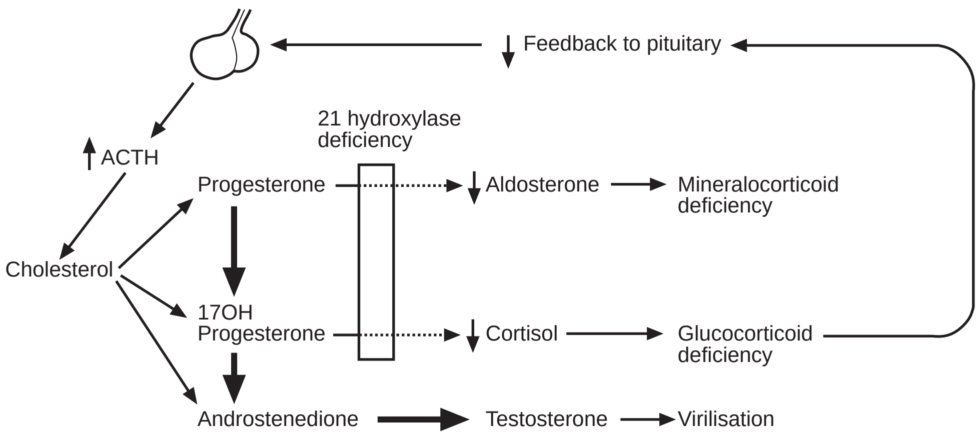
Note: In adrenal gland failure, a high level of ACTH results. Melanocyte stimulating hormone is derived from the same precursor pro-opiomelanocortin.

ADRENAL CORTEX AND MEDULLA

Congenital Adrenocortical Enzyme Defects
These are rare, inherited conditions due to autosomal recessive traits.
Each transformation step in the pathways of steroid formation in the adrenal cortex requires the activity of one or more enzymes. Deficiency of any enzyme will interfere with production of the end product.

21 hydroxylase deficiency
This is the commonest type, and the lack of this enzyme prevents the production of cortisol and aldosterone. The low blood cortisol activates ACTH secretion. Adrenal hyperplasia follows and, although cortisol is not formed, other steroids are produced in excess. The resulting clinical syndrome varies with the severity of the defect.

1. Symptoms of Addison's disease.
2. Lesser degrees of adrenal failure plus symptoms due to excess of sex steroids.
   (a) Pseudohermaphroditism in females; precocious puberty in males.
   (b) Virilism in female.
3. No signs of adrenal failure but sex disturbance, e.g. amenorrhoea, hirsutism.

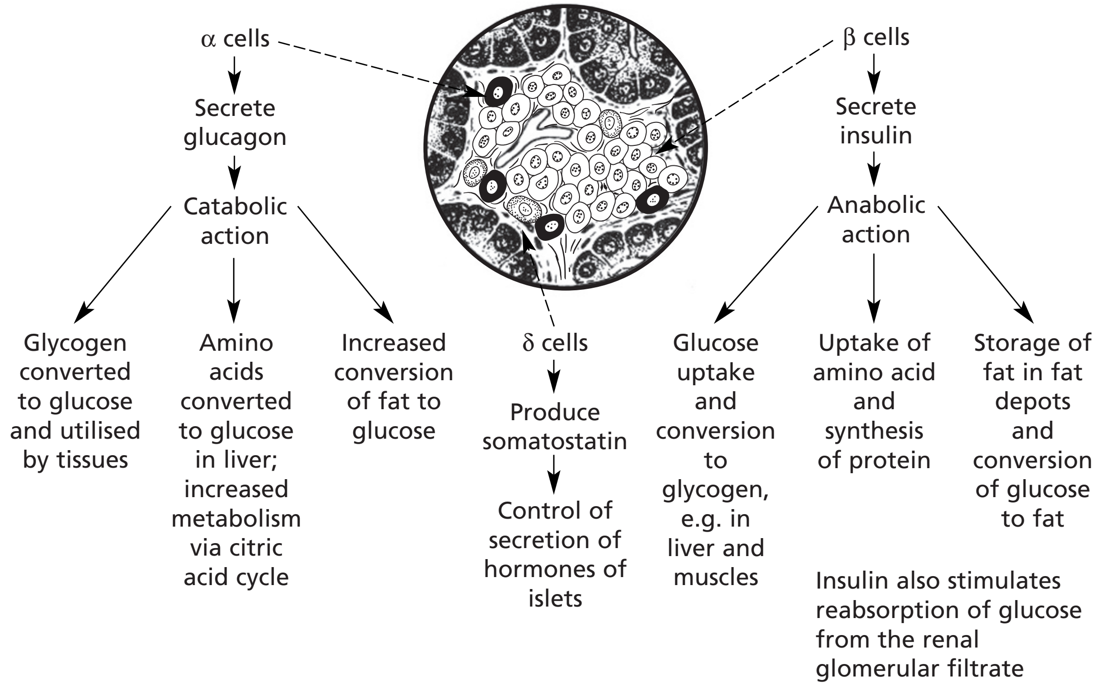


ADRENAL MEDULLA
Excess production of catecholamines may occur with some tumours of the medulla. Three are described:
1. **Phaeochromocytoma.** This tumour is composed of chromaffin cells. Symptoms are due to paroxysmal overproduction of the amines with hypertension, raised metabolic rate and blood sugar. Cerebral haemorrhage may occur. About 25% of phaeochromocytomas are familial, 10% are bilateral and 10% are malignant. It is very difficult to predict behaviour on histological grounds.
Familial cases may be associated with:
(a) MEN syndromes.
(b) Neurofibromatosis.
(c) Von Hippel–Lindau syndrome.
(d) Germ line mutations of succinate dehydrogenase genes.

2. **Ganglioneuroma:** a benign tumour, composed of well-differentiated ganglion cells (p.577).
3. **Neuroblastoma:** a very malignant tumour of primitive nerve cells, occurring in children.

ENDOCRINE PANCREAS

The islets of Langerhans form 1–2% of the pancreatic tissue. Four types of cell make up the islets. The majority are β cells.



Insulin and glucagon have virtually opposite actions. The action of insulin is also opposed by growth hormone and glucocorticoids.

The fourth type of cell is the pancreatic polypeptide (PP) cell, found in highest concentration in the head of the pancreas.

DIABETES MELLITUS

This condition is due to an absolute or relative lack of insulin activity. The American Diabetic Association classification of diabetes includes 10 categories.

There are 2 main types

Type 1 – immune mediated β cell destruction ➔ absolute insulin deficiency.
Type 2 – adult onset due to insulin resistance, and β cell dysfunction and a range of rarer causes including genetic defects of β cell function and insulin receptors, diseases of the exocrine pancreas, and gestational diabetes.

ENDOCRINE PANCREAS

BIOCHEMICAL CHANGES AND CLINICAL EFFECTS

The main results of insulin lack are:

1. **Inability to control carbohydrate metabolism, causing:**

Hyperglycaemia → Glycosuria
Hyperglycaemia ↓ Increased plasma osmolarity
Glycosuria ↓ Osmotic diuresis
Osmotic diuresis → Increased plasma osmolarity
Osmotic diuresis ↙ Hypovolaemia ↘ Loss of Na^+ and K^+
Increased plasma osmolarity → Thirst; Hypovolaemia → Thirst
Thirst → Polydipsia

2. **Increased fat catabolism**

Leads to:
↓ Excess production of acetyl CoA
→ Conversion to ketone bodies (acetone + hydroxybutyric acid)
→ Ketosis → Acidosis → Acid excreted in combination with Na^+ and K^+
↓ Further electrolyte depletion

3. **Increased catabolism of amino acids** prevents proper protein synthesis and this, together with (1) and (2) above, leads to loss of weight despite polyphagia.

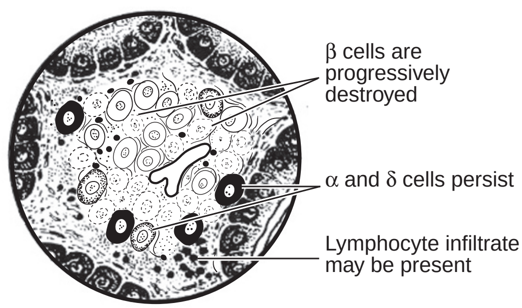
TYPES OF DIABETES

Primary forms

TYPE 1 Diabetes

This form is due to destruction of β cells in the islets of Langerhans.

The onset is acute and the peak of incidence is around 13 years. Factors of importance in the aetiology:



1. There is a familial incidence and in 80% of cases there is an association with Class II HLA antigens (particularly HLA DR3, DR4).
2. Environmental factors, e.g. coxsackie B virus, may trigger islet cell destruction.
3. Cell-mediated immunity against islet antigens and humoral antibodies are present in most cases.
   This has given rise to a theory of pathogenesis:

GENETIC SUSCEPTIBILITY – inheritance of particular Class II HLA antigens + EXTRINSIC FACTORS – ? virus infection
↓
Activation of autoimmunity → Damage to β cells → Type 1 diabetes.

Other forms of auto-antibody, e.g. gastric, thyroid, adrenal, have been demonstrated.

ENDOCRINE PANCREAS

Types of diabetes (*continued*)

Primary forms

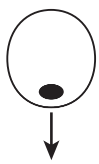
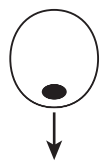
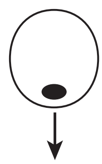
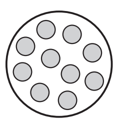
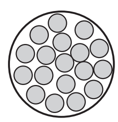
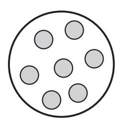
TYPE 2 Diabetes Mellitus

This is the commonest form of diabetes affecting 10% of adults over 65 in Western society. It is commoner in Asians and Afro-Caribbeans within Western societies. It is more frequent in females and the incidence increases with age. In contrast to Type 1, the onset is slow and the changes in glucose metabolism mild. (Diet restriction to reduce OBESITY and oral hypoglycaemic drugs usually control the blood sugar.) Clinical presentation is often due to complications, particularly vascular. Often the disorder is detected by biochemical screening.

Aetiology

This is a multifactorial disorder involving environmental and strong genetic factors. The basic mechanism is prolonged INSULIN RESISTANCE in the tissues leading eventually to inadequate secretion of insulin by β cells. The combination of obesity, Type 2 diabetes and hyperlipidaemia leads to an increased risk of cardiovascular disease.

The following theory accommodates the known facts:

OBESITY			
Adipocytes	 Free fatty acids	 Cytoxins	 Adipokines
Islets		 Compensation	 Failure
Insulin secretion	Normal	Raised	Decreased
Blood sugar	Normal	Impaired glucose tolerance	Diabetes

Note 1: The concordance rate for identical twins is up to 60% in some studies.
Note 2: β cells secrete islet amyloid protein along with insulin. **Amyloid** is deposited in islets in Type 2 diabetes probably reflecting the prolonged β cell activity.

ENDOCRINE PANCREAS

Types of diabetes (*continued*)

Secondary forms **(Type 3)**

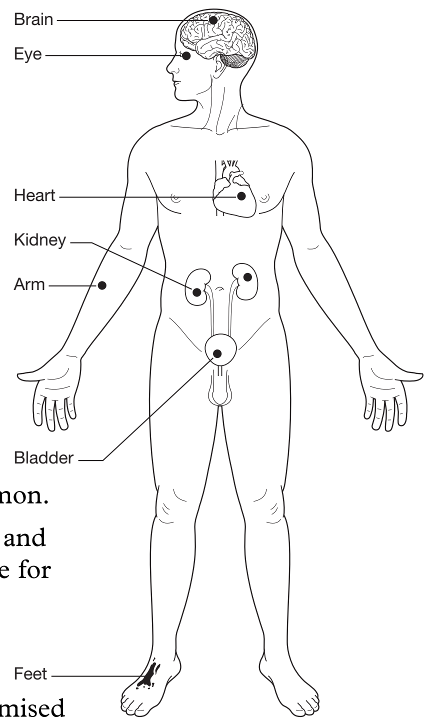
Diabetes may complicate:

1. A number of endocrine diseases (acromegaly, Cushing's syndrome, phaeochromocytoma)
2. Metabolic diseases (haemochromatosis)
3. Drug therapy (steroids, thiazide diuretics)
4. Pancreatic inflammation, etc. (chronic pancreatitis, mumps, cystic fibrosis).

Gestational Diabetes (Type 4)

This is associated with glycosuria during pregnancy and the birth of overweight babies. Control of the maternal blood sugar reduces birth weight to normal. Permanent diabetes is apt to develop at a later date.

COMPLICATIONS OF DIABETES



1. **Diabetic Coma**. 2 forms occur:

   (a) **Keto-acidotic coma.** This is common in Type 1 diabetes. Hyperosmolarity, hypovolaemia, acidosis and loss of electrolytes if unchecked lead to coma.

   (b) **Hyperosmolar non-ketotic coma.** This develops slowly in Type 2 diabetes. Hyperglycaemia builds up and produces profound dehydration.

2. **Hypoglycaemic coma.** This complication of treatment occurs when insulin intake is excessive for the amount of food consumed.

3. **Cardiovascular lesions**

   (a) Atheroma develops at an earlier age and with increased severity. Coronary thrombosis is common.

   (b) Microangiopathy causing occlusion of arterioles and capillaries. These vascular lesions are responsible for many of the clinical lesions e.g. cardiac failure, retinopathy, neuropathy, gangrene of limbs, Kimmelstiel–Wilson lesions in the kidney.

   The frequency of cardiovascular lesions can be minimised by tight control of blood glucose levels (usually by monitoring glycated haemoglobin) and blood pressure.

4. **Renal failure** is common. It may be due to glomerulosclerosis, but pyelonephritis and renal papillary necrosis are other causes.

5. **Infections.** There is an increased susceptibility to sepsis, fungal infections and tuberculosis.

6. **Neuropathy.** (a) Peripheral / (b) Autonomic } Possibly due to direct metabolic damage ± microvascular occlusion

ENDOCRINE PANCREAS

PANCREATIC ENDOCRINE TUMOURS (ISLET CELL TUMOURS)

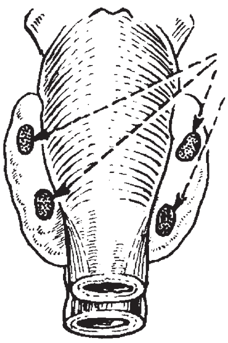
These are uncommon. Most are benign and are asymptomatic unless they secrete excess hormones. 10% are malignant. The clinical effects vary with the hormone produced.

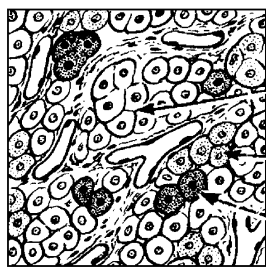
1. INSULINOMAS arise from β cells and produce attacks of hypoglycaemia.
2. GASTRINOMAS cause multiple peptic ulcers (Zollinger–Ellison syndrome).
3. Glucagonomas and somatostatinomas induce diabetes.
4. Other hormones secreted, e.g. serotin and ACTH leading to carcinoid syndrome, Cushing's syndrome, etc.

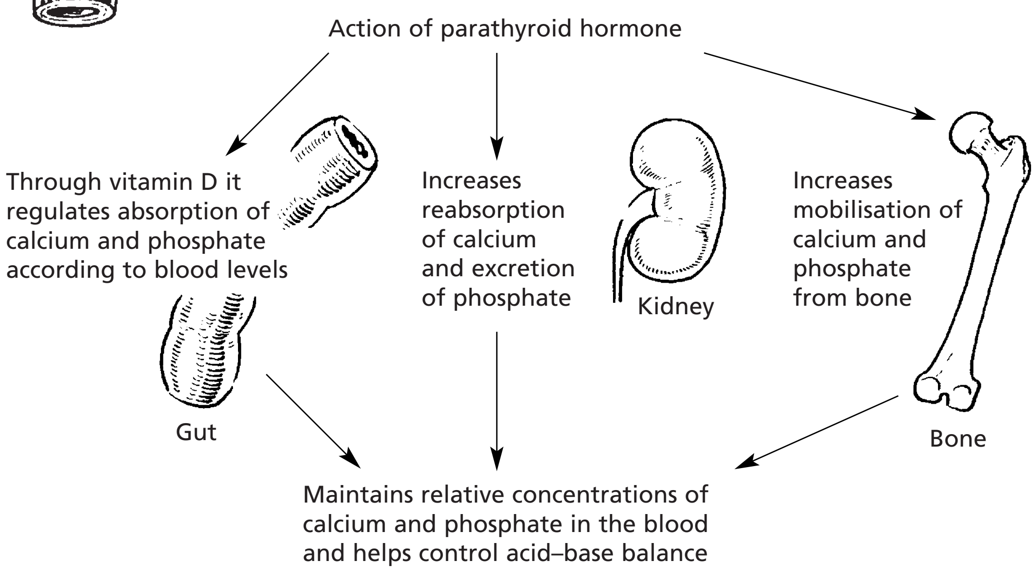
These tumours may form part of multiple endocrine neoplasia syndromes (p.643).

PARATHYROID GLANDS

The parathyroids are four small glands lying posterior to the thyroid gland.







PARATHYROID GLANDS

HYPERFUNCTION (see p.591)
There are 3 forms:

1. **Primary**
   This is due to **adenoma** (> 80%), **hyperplasia** (approx. 15%) and **carcinoma** (approx. 2%).
   The **blood calcium** is **raised.**
   The effects are:
   (a) Formation of renal calculi sometimes leading to renal failure.
   (b) Parathyroid bone disease, now uncommon
   (c) General muscle weakness.
   (d) Metastatic calcification.

2. **Secondary**
   Parathyroid hyperplasia is a response to the low blood calcium from various causes as follows:

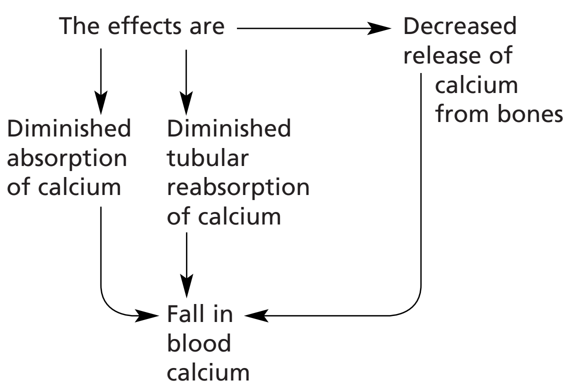
   CHRONIC RENAL FAILURE }
   Malabsorption syndromes } HYPOCALCAEMIA ⟶ PARATHYROID HYPERPLASIA
   Vitamin D deficiency }

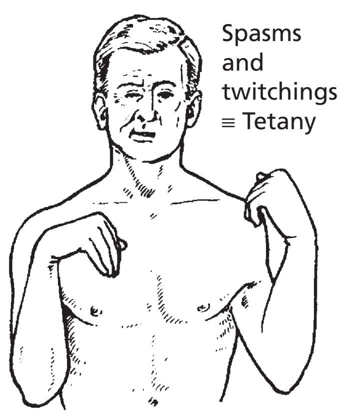
3. **Tertiary**
   In a few cases of secondary hyperparathyroidism an autonomous nodule develops in the hyperplastic gland and HYPERCALCAEMIA results.

Note: **Humoral Hypercalcaemia of Malignancy.**
Carcinomas, particularly of the lung and kidney may produce **Parathyroid hormone related peptide** (PTHrP) which causes **hypercalcaemia.**
This is not related to parathyroid disease.

HYPOPARATHYROIDISM

This occurs in 3 circumstances:
1. Surgical removal, sometimes accidentally during thyroidectomy
2. Auto-immune disease (very rare).
3. Congenital deficiency (e.g. DiGeorge syndrome).





MULTIPLE ENDOCRINE NEOPLASIA SYNDROMES (MENS)

This is a group of familial conditions (autosomal dominant inheritance) characterised by multiple endocrine tumours.

The main syndromes are:

MEN 1 – (WERMER Syndrome) Parathyroid adenoma, hyperplasia,
Pancreatic endocrine neoplasms,
Pituitary adenomas, especially prolactinomas.

This is due to mutation of the MEN 1 gene on chromosome 11, which encodes menin, a nuclear protein.

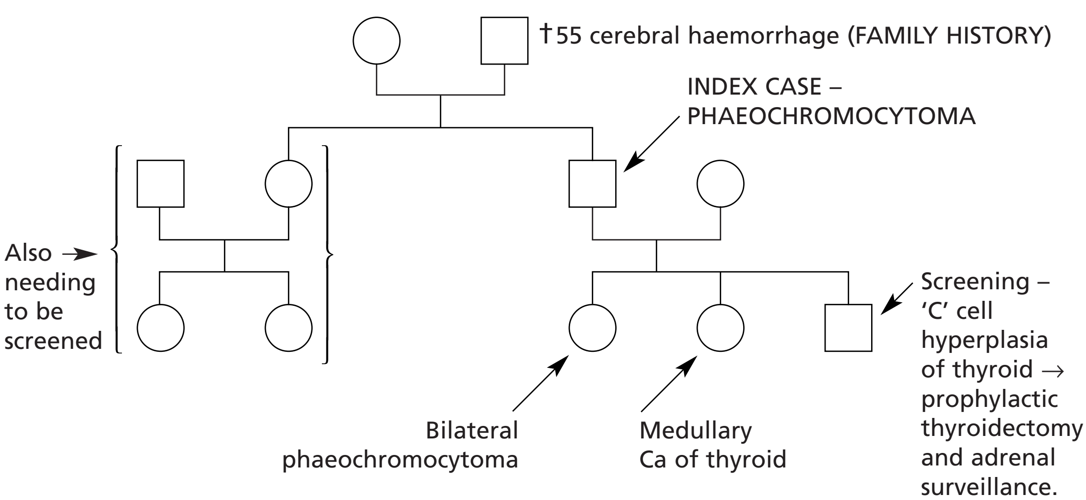
MEN 2A – (SIPPLE Syndrome) Medullary carcinoma of thyroid,
Phaeochromocytoma,
Parathyroid adenoma or hyperplasia.

MEN 2B – Medullary carcinoma of thyroid (poor prognosis),
Phaeochromocytoma,
Mucosal 'neuromas',
Ganglioneuromas of gut and skin,
Marfanoid habitus.

These are due to mutations activating the *ret* oncogene on chromosome 10 which encodes a cell surface receptor with tyrosine kinase activity.

Their importance is that family screening may pick up tumours at an early stage, indeed at the stage of hyperplasia which often precedes the development of tumours.

Illustrative family history:



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